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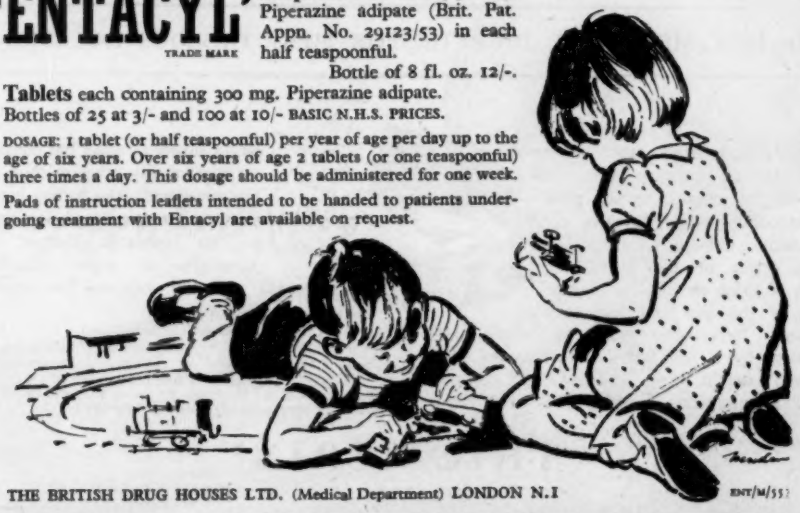
DOSAGE: 1 tablet (or half teaspoonful) per year of age per day up to the age of six years. Over six years of age 2 tablets (or one teaspoonful) three times a day. This dosage should be administered for one week.

Pads of instruction leaflets intended to be handed to patients undergoing treatment with Entacyl are available on request.



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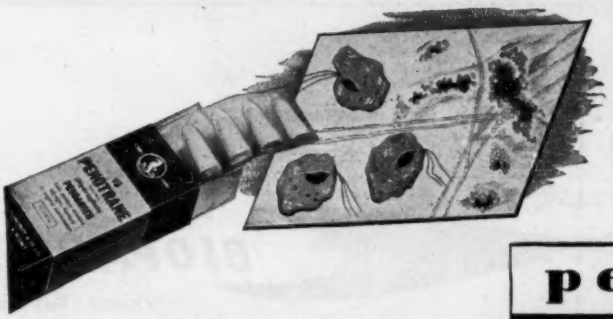

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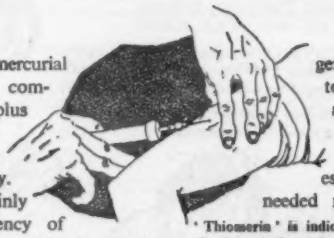

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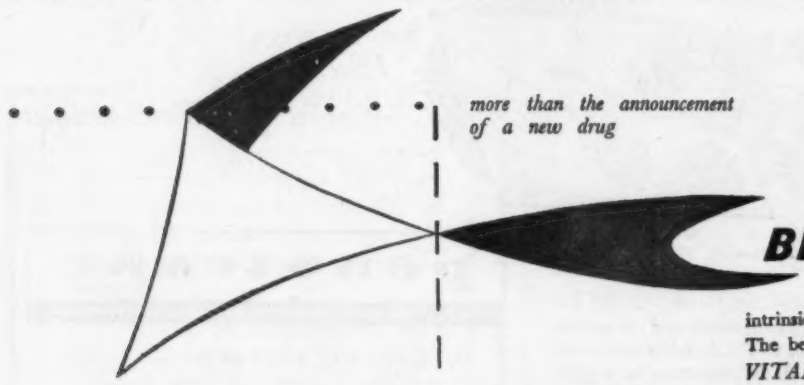

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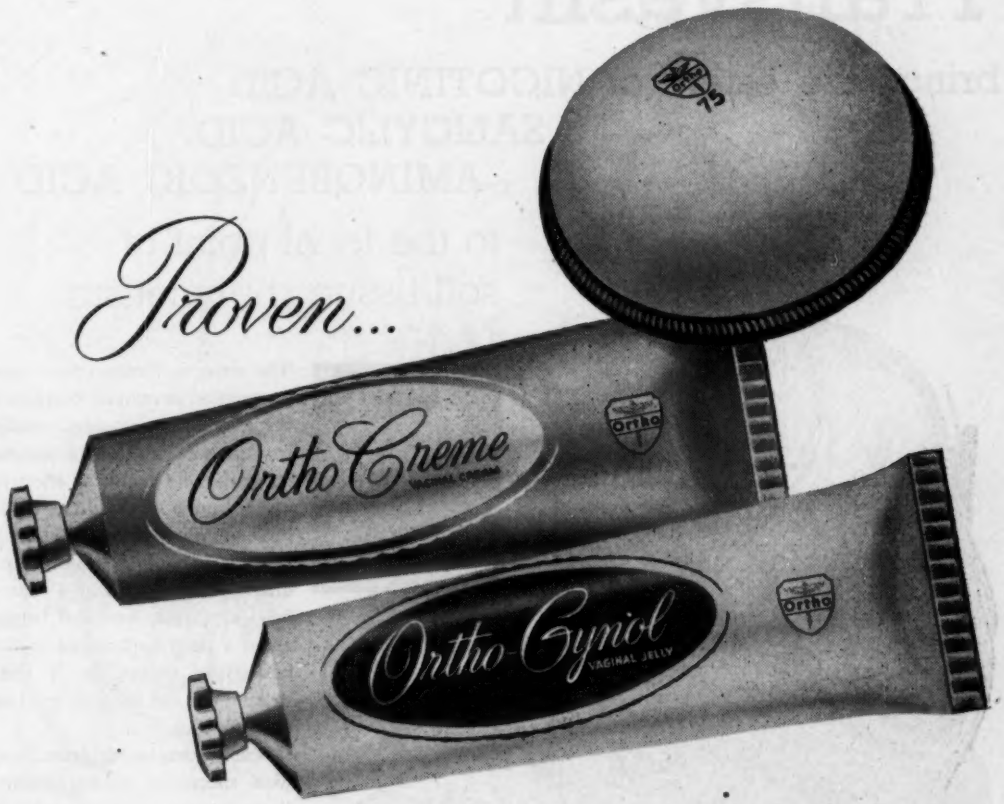

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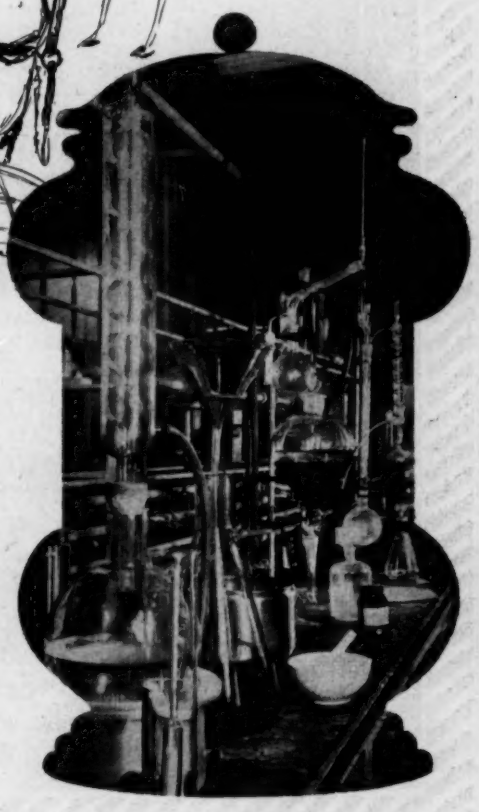

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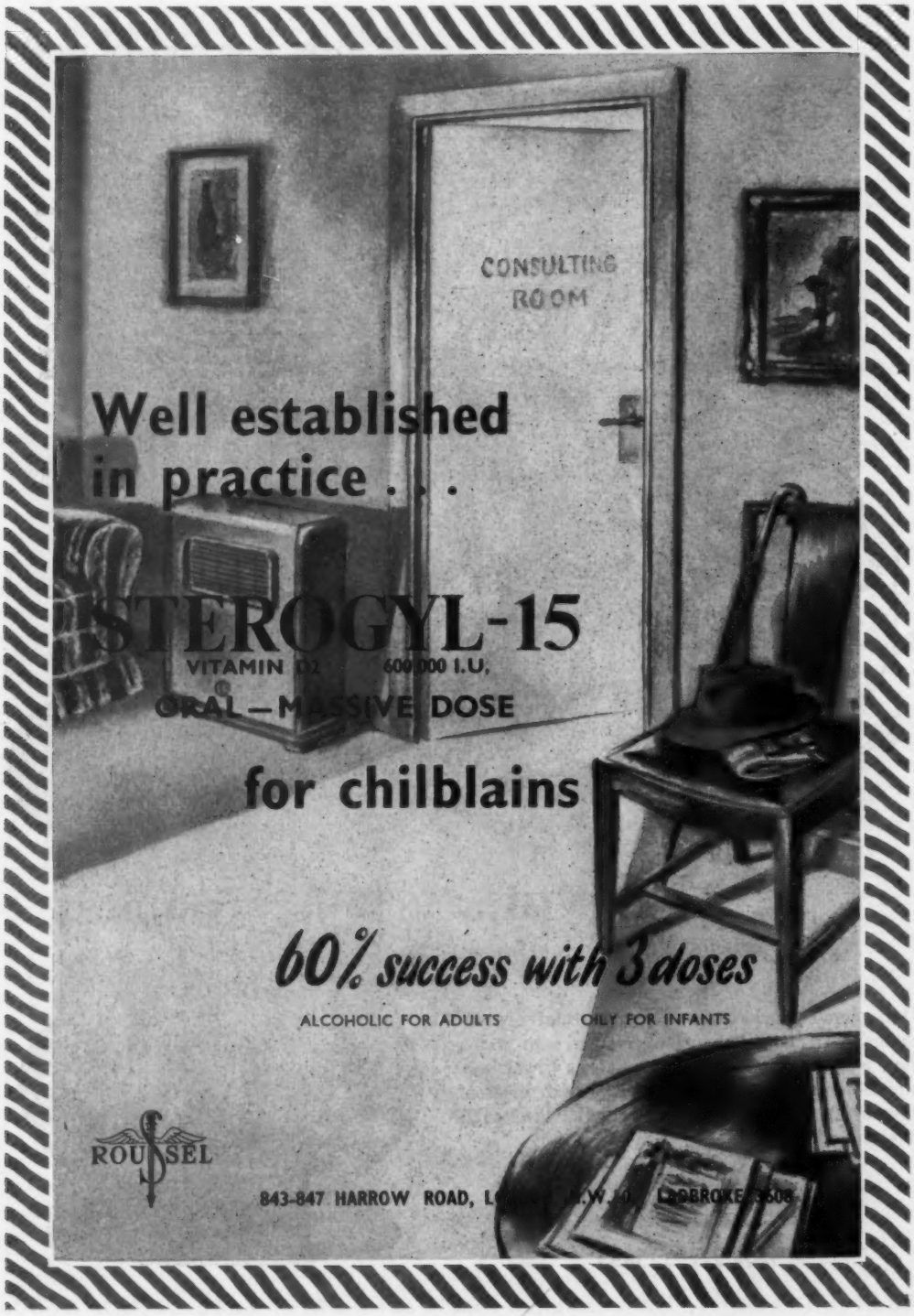
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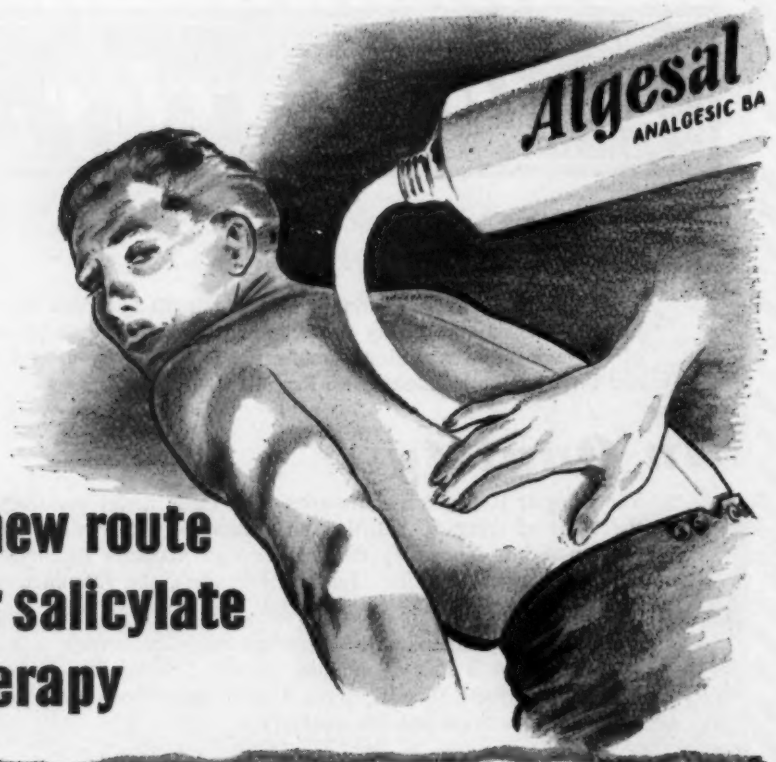

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[1] Practitioner, (1953) 170, 515.

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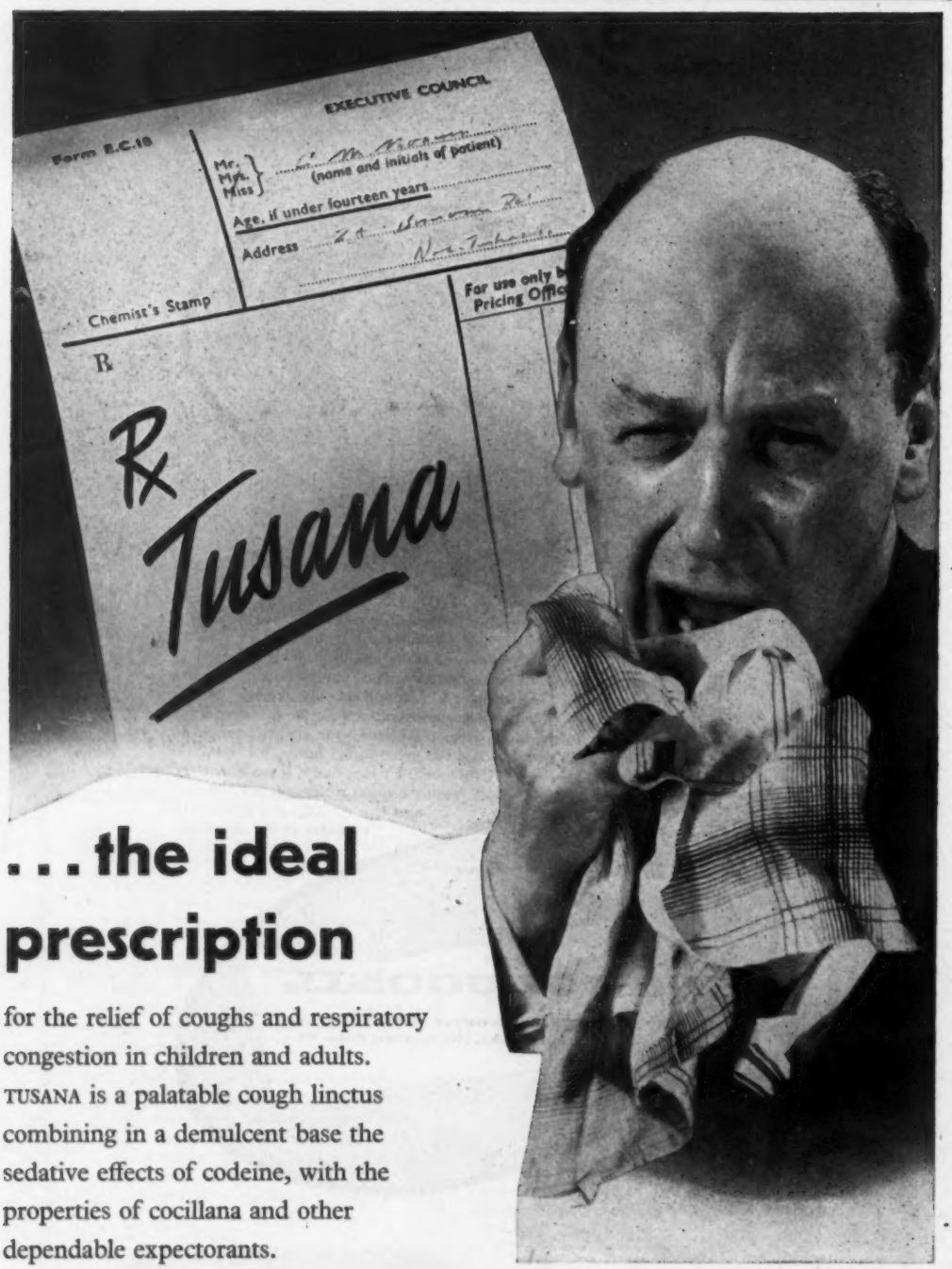

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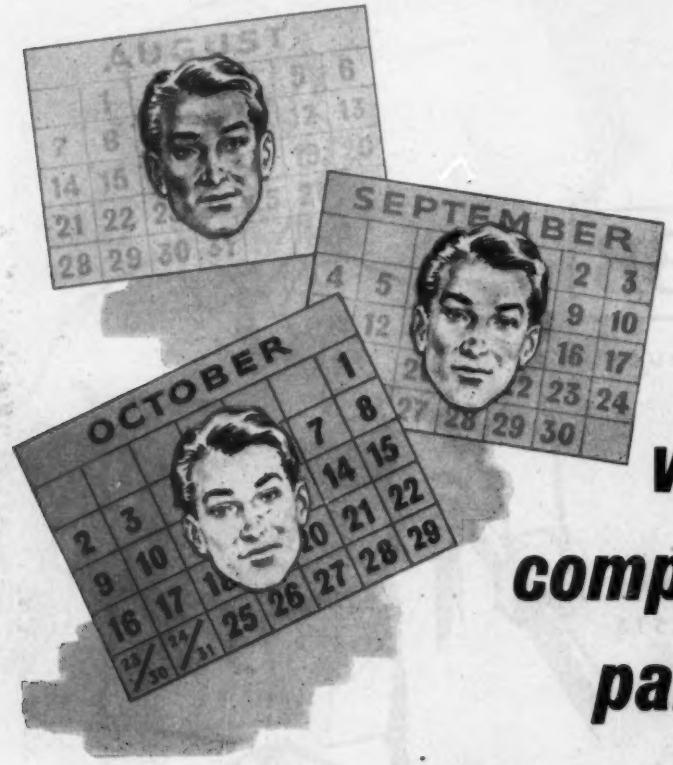

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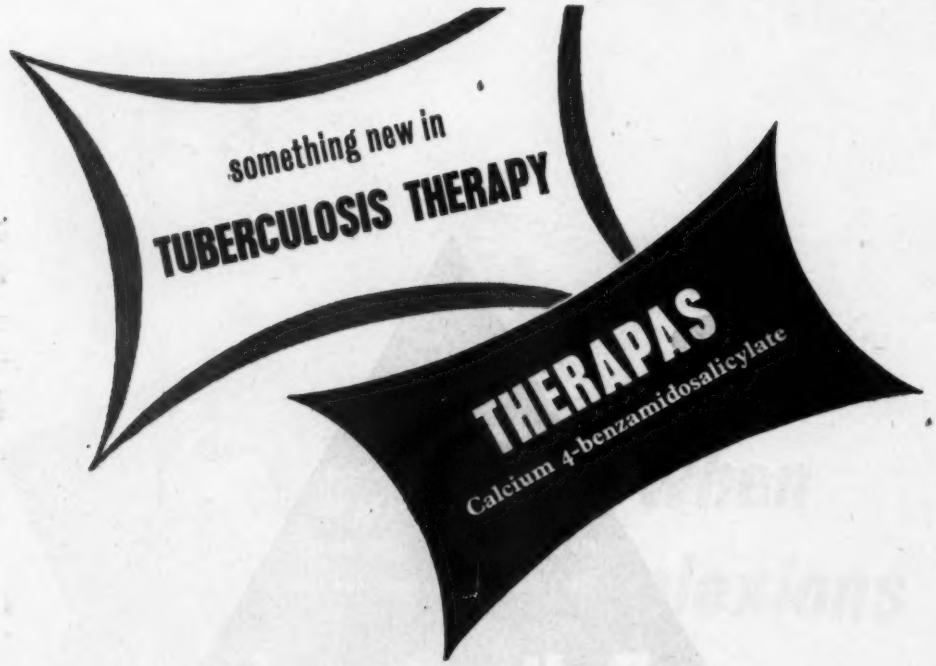

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1 *J. Pharmacy & Pharmacol.*, 1953, 5, 849
2 *Schweiz. med. Wschr.*, 1955, 85, 222
3 *Tubercle* 1955, 36, 209

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Nulacin tablets are not advertised to the public, have no B.P. equivalent and may be prescribed on E.C.10. The dispensing pack of 25 tablets is free of Purchase Tax. (Price to pharmacists is 2/-.) Also available in tubes of 12.

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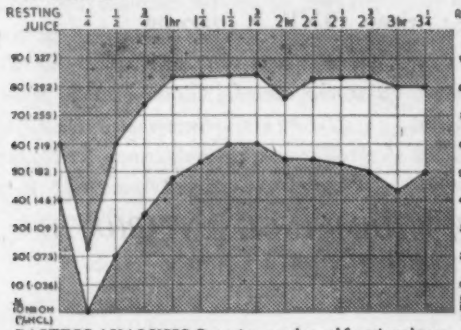
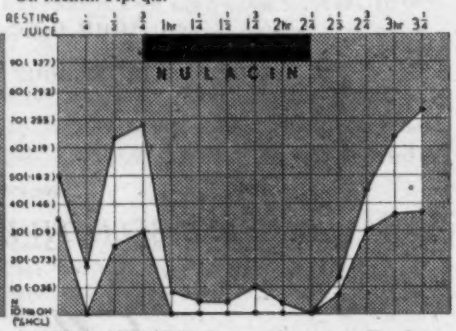


GASTRIC ANALYSIS *Superimposed gruel fractional test-meal curves of five cases of duodenal ulcer.*



GASTRIC ANALYSIS *Same patients as in Fig. 1, two days later, showing the striking neutralizing effect of sucking Nulacin tablets (3 an hour). Note the return of acidity when Nulacin is discontinued.*

BIBLIOGRAPHY

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Medical Treatment of Peptic Ulcer. *Med. Press* 27th February 1952 227 195-199
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Ambulatory Continuous Drip Method in the treatment of Peptic Ulcer. *Amer. Jour. Dig. Dis.* March 1955 22 67-71.

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A CONSTRUCTIVE REVIEW *

J. H. HUNT
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"We have to decide what the general practitioner should be doing, and then—whatever it is—enable him to do it properly."—*The Lancet*, March 25, 1950.

THE publication of the Collings report (1950)—a critical reconnaissance of 55 English practices—may well be looked upon by medical historians as a turning-point in the development of general practice in Great Britain. Its challenge has been accepted, and much is being done to put things right. In this present review, five years later, several matters of importance for the future of general practice are examined (the opinions expressed being purely personal) in an attempt to be constructive and to stimulate further *experiment* before irrevocable decisions are made. The need has never been greater for carefully planned investigations into the aspects of general practice discussed in the following pages.

Important changes are about to take place which will lead to a closer integration of general-practitioner and hospital services. Crowded outpatient departments and shortage of hospital junior medical staff might be remedied by enlisting the help of family doctors in the work of outpatient departments. The same result would be better achieved, however, by giving general practitioners more help and encouragement to diagnose and treat their own patients themselves before sending them to hospital, and by increasing the number of general-practitioner beds. Of these two remedies, reasons are put forward for believing that the second is far more important than the first, because a family doctor's first duty is to care for *his own patients* at home, in the surgery, and sometimes in hospital, before he does specialised work or helps consultants in outpatient departments to treat the patients of other doctors.

Changes in the Scope of General Practice

The general practice of medicine, or "family doctoring," must be nearly as old as man himself. For thousands of years nearly all physicians were general practitioners; many of the great figures in medical history have been family doctors and many of the best traditions of our profession have developed around them. With the recent trend towards specialisation these facts may sometimes have been forgotten, but the pendulum which has swung so far towards the specialties during the last fifty years has now begun to swing back again towards general practice.

As Collings pointed out, we cannot expect to recapture the 20th-century concept of a 19th-century family physician—benign, bewhiskered, and beloved, with his silk hat and frock coat, leisurely driving round his practice, treating most of his sick patients himself and referring few to hospital. That way of life had many good and enviable points; but the telephone, motor-car, laboratory bench, X rays, taxation, and the National Health Service have inevitably changed many of them. The status of family doctors was at its height in this country about a hundred years ago, when their power to help their patients, through knowledge based on scientific fact, was far less than that of practitioners today. Why were many of them so highly regarded at that time? It was largely because of their strength of character, kindliness, clinical acumen, and wisdom in applying their often empirical knowledge. The deep insight into family life and character given by the work of the general practitioner remains paramount to this day, so that his rôle as friend and adviser may still far outweigh, in importance to some families, his purely medical responsibilities.

A century ago there were few specialists; medicine altered little from year to year, and it was comparatively easy for a doctor to keep up to date. Now it is very different. Thirty or more different specialties make it difficult for him to keep pace with even major changes; yet he should have a broad understanding of them all and be ready to transmit to his patients the benefit of every important advance. How much he needs to know about each development varies with different types of practice, and with the different specialties. The doctor of a boys' public school, for instance, must be up to date in epidemiology but can forget his gynæcology. Advances in dermatology, in the treatment of allergic diseases, and in ear, nose, and throat work, play a larger part in the average general practitioner's life than do those in thoracic surgery, plastic surgery, or radiotherapy.

Nowadays it is essential for the family doctor to look at his own task carefully and define his own sphere of useful activity, so that he may refer to others work that he should not attempt, while making sure that what he decides to do himself he does well. For this he needs certain indispensable personal qualities—so well described by Ronald Gibson (1955) in his recent delightful paper—and also knowledge, skill, enthusiasm, equipment, and time. How many of these has he in full measure now?

There are about two hundred and fifty common disorders which an ordinary general practitioner may expect to meet on an average at least once a year. They do not cover the whole of medicine but they include a significant and important part of it, and they are the diseases which he should be sure that he can diagnose as far as possible himself, and treat efficiently, with the minimum of specialist assistance. Modern remedies enable him to treat in a patient's home, in the surgery, or in a general-practitioner bed in hospital, many major illnesses which he was powerless to alleviate a few years ago. Under present conditions more patients have to be sent into hospital for specialist investigation and treatment than formerly, but the family doctor's obligation does not end there: he must see and treat them before they go and after they return, and over the years he is responsible for most of their medical care.

It is not always easy to appreciate what general practice, interpreted in its widest sense, comprises, or how many different types there are. In isolated places, far from consultants, some general practitioners may have to do their own emergency medicine and surgery—treating a patient who has had a hæmatemesis or a fractured femur, performing an appendicectomy (perhaps even resection of gut when the "acute appendix" turns out to be something else) or a cæsarean section. At the other end of the scale doctors in industrial areas, who see dozens of patients in their consulting-rooms each morning, may find it difficult to carry out any time-consuming investigations or treatment themselves, even those that are well within their competence; they may, indeed, have to send all their minor surgery to the local hospital. There are school doctors; factory doctors; Army, Navy, and Air Force doctors; ships' doctors; prison doctors; doctors in the Colonial Medical Service; missionary doctors; and many others—all "family doctors" of some sort or another, *in direct touch with patients* and with some period of *continuing*

* Based on a paper read in Belfast on April 23, 1955.

responsibility for their medical care—the two outstanding characteristics of general practice.

The Training of General Practitioners

Before long the profession and the medical schools will have to decide whether they take the advice of the Goodenough Committee or that of the Cohen Committee on the training of medical students; or whether, as seems likely, they will compromise and try to make the best use of both.

The Goodenough Committee (1944) said about *undergraduate* medical education:

> "In deciding the importance that should be attached to the various subjects and the type of instruction that should be given, the bias should be towards the needs of the future general practitioner."

If this is agreed, it seems reasonable that some general practitioners should help in the teaching of medical students (*British Medical Journal* 1953a). The General Medical Council is now considering this matter in its deliberations on the medical curriculum.

On the other hand, the Cohen Committee (British Medical Association 1950) laid stress on *postgraduate* education for future general practitioners:

> "General Practice is a special form of practice which must be founded on general basic principles and appropriate postgraduate study."

If that is agreed, and the vocational training for general practice is to be left to the postgraduate period, general practitioners will have an even greater part to play in teaching the "trainee-practitioner."

Departments of general practice in medical schools might be developed to advise upon and coördinate the teaching of those subjects which are important to family doctors, arrange lectures by general practitioners, and organise visits of students to general practices. Such a department could ensure that medical schools are kept in touch with modern trends in general practice; it could advise the newly qualified on the problems of the preregistration year and trainee-practitioner schemes; it could help in the planning of postgraduate courses and in general-practitioner research; it could assist in the selection of medical students, keep old students in touch with their medical schools, and help them to find appointments in general practice and, later on, suitable assistants or partners. There would be a great deal of useful work for such departments of general practice in teaching hospitals, to ensure that the right men and women are chosen for family doctoring and that they are trained in such a way that they will be able to carry out efficiently, throughout their careers, anything that future general practitioners may be asked to do. The patterns of such departments would be different from those that are being developed in the U.S.A. (American Academy of General Practice 1954, Truman 1955) or in Canada (Pollach and Solursh 1955). Details would need careful planning, and several experiments could be carried out by medical schools.

Good use could be made of more *general-practice teaching units*, like the one directed by Richard Scott (1950, 1953) in Edinburgh, which already does many of the things mentioned in the last paragraph.

Entry into General Practice

There has been considerable discussion lately about the difficulties which young men and women find when they try to enter general practice, especially those who have worked as registrars in hospitals and have gained higher qualifications. It has been said indeed that a higher qualification may prove a disadvantage, because to work for an examination in the sheltered atmosphere of a hospital is not the most effective training for family doctoring. This is not really so. Practitioners often welcome those with higher qualifications *so long as they know about general practice as well*, and this knowledge is best gained as a "trainee-practitioner" (trainee-assistant) or as an assistant. A family doctor looking for a partner wants someone who can help him in his day-to-day (and night-to-night) routine duties—visiting patients, prescribing, taking responsibility for accidents and emergencies (bandaging, dressings, and other first-aid), delivering babies, dealing with anxious relatives, and treating the many minor ailments of which so much is seen in practice. Of two candidates with equal experience of general practice the better qualified is generally successful; of two candidates with unequal experience, the one who knows most about family doctoring is usually chosen.

Some registrar appointments provide good preliminary training for general practice, especially those in general medicine, infectious diseases, dermatology, E.N.T., casualty surgery, pædiatrics, midwifery, and gynæcology. Encouragement should be given to young men and women, who can afford the time, to spend a few extra years in hospital learning one or more subjects well. The plan to provide married quarters for resident doctors in hospitals will help a few.

It may be difficult, financially and otherwise, for those who have been qualified for a while and who have been doing a registrar appointment in hospital, to spend a further year in practice as a trainee-practitioner (trainee-assistant). In Inverness a scheme is being tried under which senior house-officers spend part of their time assisting in general practice. The Oxford Regional Hospital Board is providing rotating internships, at senior-house-officer or registrar level, designed to fit the recently qualified for general practice by giving them experience in a number of specialties. St. Bartholomew's Hospital in London is making a similar plan for two senior-house-officer appointments.

If more ways can be found by which house-officers, registrars, and senior hospital medical officers can gain some experience of general practice while they are working in hospital, perhaps by spending one or two sessions a week with a family doctor, and if such experience can be officially recognised, the entry into general practice of these men and women with hospital experience will be made easier.

Group Practice

Group practice is on the increase, and it is as well to remind ourselves occasionally how a group-practice partnership differs from an ordinary partnership of three or more doctors, and what are its advantages and limitations. Doctors in ordinary partnership have surgeries in separate houses, perhaps scattered round a district; those in group practice work mainly from a single, central practice building (Ollerenshaw 1953). There are many advantages in this concentration of surgeries: it is easier to provide ancillary help (cleaning, receptionist, secretarial, nursing, dispensing, &c.), telephone cover, and even a small laboratory to be used by one or more of the partners; it is easier for one doctor to take the surgery of another who is off duty or ill, for one of the group to run an antenatal or postnatal clinic, and for an assistant to help several partners when surgeries are heavy; partners can meet more frequently and consult with each other over difficult cases, they can more readily find time for work in local-authority clinics or hospitals, or become general-practitioner specialists; and many a doctor's wife prefers the surgery away from home. The practice building may advantageously be placed near local-authority clinics, or a general-practitioner hospital.

Many districts are unsuitable, however, for this concentration of surgeries, because patients would have to travel too far to reach their doctors; and the patients must be the first consideration. In future the distance to be travelled by patients may largely determine

whether surgeries are scattered or centralised, or whether there may not be a need for both in a large partnership covering a wide area. Personality differences are more likely to occur when all partners are working under one roof; and if the temptation to "pool" lists or "zone" work is not resisted, group practice may become rather more impersonal than an ordinary partnership. The resources of few, if any, group practices in Great Britain can provide for a laboratory doing more than the simplest pathological investigations, an X-ray apparatus with a radiographer, or a minor-operations theatre properly equipped and staffed. Group practice is by no means the answer to all our problems.

Health Centres

The National Health Service was partly based on the idea of health centres. Since the start of this service, seven years ago, only five new health centres have been opened in England and Wales, and they are used by fewer than thirty general practitioners. Three others are provided by the Nuffield Provincial Hospitals Trust, and about a dozen are in various stages of development. In Scotland there are two.

This long delay in the development of health centres has had several causes. As defined by the National Health Service Act they are too rigid. They have proved formidably expensive to build and difficult to staff. One of the larger centres cost £180,000, and even the largest serves only a few general practitioners. The doctors who join a centre and have consulting-rooms in the building cannot always be sure that the premises they have vacated may not be taken over by other practitioners, who will thus annex some of their patients. The doctors who do not join but continue to work nearby tend to feel that those in the centre have special advantages and privileges. Another drawback is that health centres in England and Wales must be owned and controlled by local health authorities: many practitioners believe that if they enter such a centre they will endanger their professional liberty, they will have little say in choosing their future partners, and that other people will control their destinies.

This disappointment is a warning that careful thought and experiment, along the lines of the farsighted and valuable investigations of the Nuffield Provincial Hospitals Trust, will be necessary in future before big decisions are made about general practice. There is an urgent need, now, to develop something rather different from the health centre.

Diagnostic and Treatment Centres for General Practitioners

"FAMILY MEDICAL CENTRES"

Among family doctors in this country there is a wealth of skill and craftsmanship which is being only half used. Capable men and women, willing to take responsibility, are in many places unable to do so because they lack ready access to a few simple aids which would enable them to diagnose and treat their patients themselves. The diagnostic and therapeutic needs of even the most junior doctors working in hospitals have been recognised and provided for. Similar needs exist among doctors in general practice. Direct access to diagnostic departments in hospitals only, perhaps several miles away, is a great help but it does not solve the problem completely.

Many believe that a better service could be rendered by family doctors in some places in this country if they could use diagnostic *and* treatment units open to *all* practitioners in the district, *working from their own surgeries* (whether they be single-handed, in partnership, or in group practice). Such a unit would be situated at a central point convenient to patients and doctors, perhaps near the local shops; it would contain a room for dressings, injections, diagnostic catheterisations, and all other nursing help; a minor-operations theatre and recovery room; a pathological laboratory; and a room for consultation with local-authority workers (health visitors, district nurses, midwives, &c.). The size of the centre would depend on the number of doctors and patients needing it. If no doctor had his surgery in the building, no-one would be favoured and the centre would be used more readily by all.

In the larger centres there could also be an X-ray plant, an electrocardiograph, accommodation for maternity and child-welfare and other clinics, school medical and dental services, physiotherapy, rehabilitation, chiropody, and a room in which consultants could see patients by invitation.

In some towns, general-practitioner hospitals (cottage hospitals) provide a happy solution to the problem of coördinating the medical services of the district. In others, some of this diagnostic and therapeutic help is already given to family doctors (or could be given to them) in a general hospital, or perhaps in a general-practitioner branch or annexe of such a hospital. In places far from a hospital, however, a "family medical centre," with its integration of general-practitioner, regional-hospital-board, and local-authority services, would be invaluable. Its staffing, administration and finance have been discussed elsewhere (Ollerenshaw and Hunt 1954).

At least one diagnostic unit for general practitioners was in use in England before the introduction of the National Health Service (Hunt 1951). It has now been working satisfactorily for ten years, and its pathological laboratory and X-ray department have been used by many practitioners in the neighbourhood. More recently the centre at Corby (*Lancet* 1954), which has been developed under the auspices of the Nuffield Provincial Hospitals Trust, was opened in April, 1954. It has many of the characteristics of the family medical centres described above, except that the local-authority health services are not, as yet, incorporated in it. This centre is running successfully and those who are interested in this problem should visit it.

Should family doctors perform minor surgical operations? As Stephen Hadfield (1953) and Stephen Taylor (1954) have pointed out in their surveys, only a few general practitioners seem to wish to do so under present conditions. Family doctors should not treat serious whitlows without specialist help if there are surgeons within reach, nor should any but the fully experienced perform major operations. The Walker report said, however,

> "The habitual transfer of minor surgery to the hospitals is neither necessary nor desirable. The training of the doctor has included instruction in this work and, in the view of the Committee, it is part of general practice." (*British Medical Journal* 1953c.)

Students are taught minor surgery; all house-surgeons perform minor operations; so do casualty officers and surgical registrars in the theatres provided for them. Many of these enter general practice, yet only a small proportion of family doctors in the British Isles have access at present to a properly equipped minor-operations theatre or are helped by anæsthetists. The more surgical experience a doctor has had, the less anxious will he be to operate without proper equipment. In an area in South London there are eighty-seven general practitioners working within five square miles; so far as can be ascertained not one of them has entry to a minor-operations theatre. The risk of litigation may discourage some doctors from doing this work. This risk applies, however, to almost everything a doctor does. For those who are properly trained, conscientious, and skilled in that which they undertake, it is less of a deterrent than is sometimes supposed. It may be necessary to find some method of rewarding general

practitioners for minor surgery, as we do those who are responsible for midwifery.

The general practitioner's need for access to pathological and radiological departments is now being increasingly recognised, and an attempt has been made to satisfy it in hospitals throughout the country. The use of these hospital departments by practitioners, however, is less enthusiastic than might have been expected (Ministry of Health 1953, p. 25). What is not always realised is that a hospital department several miles away is not nearly as valuable to a family doctor as a smaller laboratory or X-ray apparatus near by. There he can drop in to see the slides and X-ray films, chat with the technician or radiographer, or consult with the clinical pathologist or radiologist who can attend once or twice a week and supervise the department. *Personal contact* is the crux of the matter. *Supervision* is essential: every laboratory should be visited at regular intervals by a pathologist, and every X-ray film should be reported upon by a radiologist, but the family doctor will often wish to see the slides or the X-ray films, in the first instance himself, to help him decide on immediate treatment.

At present the number of these small laboratories might be limited by lack of technicians, but more could be trained. Much of this work is being done all over the world by girls of secretarial status; it does not take much longer to teach an intelligent girl how to do a blood-count, a blood-urea, and a blood-sugar test, than it takes to teach her to become an efficient and fast shorthand-typist. Each technician could be on the extramural staff of the nearest hospital, and could keep up to date by doing part-time work in the hospital laboratory or X-ray department, or by returning to full-time work in the hospital at intervals.

The development, in future, of diagnostic and treatment centres for the use of general practitioners near their surgeries would meet a real need in many areas far from hospitals. In few hospitals, even, at present can a family doctor drop in with a swab and see the smear himself under the microscope, talk with the pathological technician or pathologist, watch a dressing being done by a nurse on one of his patents, do a minor operation himself, look at an X-ray film with the radiographer or radiologist, and discuss a point with a health visitor or another with a practitioner colleague—all at one visit. This is the type of personal contact and coöperation, of such real value and which saves so much time, which could be fostered so easily in a family medical centre. Many practical difficulties in the development of such centres will be met, but none of these should be insurmountable. Further experiments on the lines of those sponsored by the Nuffield Provincial Hospitals Trust at Corby, Harlow, and Manchester, with modifications to suit local requirements, should prove well worth while.

General Practitioners in the Outpatient Departments of Hospitals

There has been controversy lately about general practitioners doing work in the outpatient departments of hospitals, and whether they should be encouraged to do so. A recent increase in outpatient attendances and shortage of hospital junior medical staff have brought this matter to the fore. The latest published figures show that there are over 38 million hospital outpatient and casualty attendances yearly in this country (Ministry of Health 1953) and that more than eight hundred house-officer and registrar appointments are vacant (*British Medical Journal* 1955).

Can general practitioners find time to work in hospitals? The primary responsibility of a family doctor is that he should help his own patients in any trouble at any time, day or night. To fulfil this obligation, many doctors in the past have had to be on duty in their practices twenty-four hours a day, six or seven days a week, for about forty-eight weeks a year. This has sometimes been bad for their efficiency, their health, their family life, their recreation, or their continuing education. The modern attempt to solve this problem is by the development of larger partnerships, group practices, and rota systems, to satisfy the patients, the doctor's conscience, his wife, his children, his golfing friends, and still allow him time to keep up to date by reading, attending medical meetings and doing a little work with his colleagues in hospital.

Are practitioners capable of helping in the outpatient departments of hospitals? There are many appointments in the outpatient departments of hospitals which family doctors, apart from those who are recognised as "general-practitioner specialists" (see below), can fill for their own benefit and postgraduate training as well as to help the hospitals, and in which they can take some degree of responsibility—such as in clinics for infant feeding, antenatal and postnatal work, skin diseases, diabetes, allergic diseases, rheumatic diseases, geriatrics, and dietetics. There are general practitioners who like this type of outpatient work and are good at it; when they have gained experience their colleagues soon recognise and respect their special knowledge, and are willing to make use of it. In teaching hospitals, students and house-officers help in outpatient departments; in other hospitals, there is no reason why general practitioners should not do the same as an important part of their continuing education, in collaboration with consultants, so long as they are prepared to work conscientiously and deputising arrangements in their practices allow them to attend regularly and punctually.

There are two main difficulties. Firstly, patients in a practice do not like being left too often under the care of a partner or assistant. Secondly, when a family doctor sends a patient up to hospital for an opinion, he may not want a general-practitioner colleague (maybe a competitor from an opposing partnership who is not recognised as a general-practitioner specialist) to advise on the case and perhaps point out an omission or mistake. This does not often happen, but it seems to do so more frequently in general medical and surgical outpatient departments than in special departments. When it does occur it is, admittedly, a real objection which must be overcome.

Many practitioners in this country are already doing useful part-time work in the outpatient departments of hospitals as clinical assistants (voluntary or paid), or in other appointments, without necessarily regarding themselves as "specialists." There are as many gradations and as little difference in status between the truly "general" practitioner and the general-practitioner specialist, as there are between the general consultant (medical or surgical) and the consultant specialist (a consultant in a single specialty).

Hospitals, family doctors, and all their patients will benefit if these part-time appointments of general practitioners to outpatient departments of hospitals are extended in the right way. General practitioners (apart from general-practitioner specialists) will no doubt apply eagerly for these posts in future if the duties, responsibility, title, status, and remuneration are attractive and if they are restricted to one, or at most two, sessions a week. If some of these appointments are "rotating" so that doctors work in different departments of the hospital, changing perhaps once a year, this will help them to gain experience and keep up to date in many fields, though it may not be as useful to the departments concerned as appointments for a longer term.

It must be remembered, however, that in outpatient departments general practitioners see mostly other doctors' patients and not their own. This part-time work in hospitals must not be allowed to interfere

materially with a doctor's practice; neither must it upset in any way the development of diagnostic and treatment centres outside hospitals, nor the provision of more general-practitioner beds, both of which are badly needed to help family doctors look after their own patients better.

General-practitioner Specialists

The real need is to produce more good general practitioners and to make the good ones better still. If there were enough consultants and specialists throughout Great Britain and the Commonwealth to do all the work in the special departments of all the hospitals, the general-practitioner specialist might not be required. Every general practitioner could then aim at being a good general doctor, as many would prefer. There are, however, not enough consultant and specialist appointments for this, and it is unlikely that there ever will be; so that some family doctors, whether they want to or not, may have to continue to do a certain amount of specialised work. For this reason the borderline between general practice and specialist practice may never be clear-cut.

In the past certain general practitioners, who by intensive study and practice have developed particular interests, have become recognised as "general-practitioner specialists" in medicine, surgery, anæsthetics, midwifery, pædiatrics, public health, and so on. Like registrars in hospitals, they have been looked upon as specialists rather than consultants. How many of them have been needed in a partnership has depended largely on the number of consultants within range. In parts of England now, especially in the cities, they are not needed so much as they were: in other parts of the country, however, remote from large centres, and in places abroad, they are still essential and are doing excellent work. Some partnerships in Canada, Australia, Africa, and the U.S.A. are largely made up of them.

Their training needs to be somewhat different from that of their partners. Many of them acquire a postgraduate diploma. It is helpful for those doing surgery, medicine, or midwifery to hold the diplomas of F.R.C.S., M.R.C.P., or D.OBST., and for those doing anæsthetics or public health, the D.A. or D.P.H.: this applies to all postgraduate diplomas that are within the reach of general practitioners. To ensure a high standard it may prove necessary, later on, to make such a postgraduate diploma obligatory for those who wish to be recognised as general-practitioner specialists.

The name "general-practitioner specialist" is, in some ways, a contradiction in terms; yet it is useful and its meaning is clear. General practice remains his chief responsibility but he voluntarily takes up, in addition, a special subject which can be mentioned in parentheses in his title—general practitioner (surgeon), (obstetrician), (anæsthetist), (pædiatrician) and so on.

The family doctor is achieving more responsibility and autonomy in his own subject—general practice. If he is to go on playing his part in the specialties (as a specialist rather than as a consultant), it should be as a member of a team of which the more senior members will be consultants to whom he may turn for help and advice, and to whom he can refer difficult or unusual cases. The more junior members will be the house-officers and other hospital junior medical staff. In the past the need for this team-work was not always fully realised or properly provided for, and the troubles that sometimes arose out of the work of general-practitioner specialists were due to their working alone, out of touch with those who could have helped them. Nowadays this team-work and supervision should be easy to plan in most parts of the country; many regional hospital boards have, indeed, already arranged it. Even in isolated parts of the Commonwealth, air travel and other forms of transport should make it feasible.

The Specialist Team

The duties of the various members of this specialist team will differ. The *general-practitioner specialist*, living perhaps in a small town, will limit the scope of his special work, give what time to it that he can spare from his general practice (perhaps four sessions or so a week), and attempt only that part of a specialty that he can do well. If he does this strictly, he will be able to keep within his capacity and will make few mistakes. Further experiments are needed on possible ways of ensuring not only this limitation of his special work, but also adequate supervision. His special cases will come to him outside hospital largely from his own partnership or group, with maybe 10,000–20,000 patients between them. In hospital, they may also come from other doctors in the neighbourhood: ways will have to be found to prevent the patients of these other doctors transferring themselves to his practice. In a large group practice, made up of several general-practitioner specialists, some patients may find difficulty in obtaining specialist advice outside the group; this, too, must be overcome. The success of a more widespread general-practitioner specialist scheme will depend upon a satisfactory solution of these problems.

The special interests of the *general consultant* (physician, surgeon, or obstetrician-gynæcologist), from the larger town, will cover a much wider range. He will never be replaced by general-practitioner specialists or by those working in narrow specialised fields. If the number of general-practitioner specialists is increased, more general consultants will be needed and more will be asked of them.

The work of the *consultant specialist*, in the largest town and cities, will encompass the whole field of a single specialty such as ophthalmology, dermatology, orthopædics, neurosurgery, chest surgery, anæsthetics, oto-rhino-laryngology, psychiatry, pathology, radio-diagnosis, radiotherapy, and so on.

In many districts there will be need for all three types of "specialist" working together in close coöperation, helping each other. Their duties must necessarily merge into one another and overlap to some extent; it is important that this unavoidable overlap should be recognised, and that allowance for it be made on all sides when delicate situations arise.

It is possible that general practitioners will be invited before long to do more special work in hospitals as general-practitioner specialists. Apart from relieving the hard-pressed outpatient departments, this arrangement will help to solve the "registrar problem" by enabling registrars and senior hospital medical officers to continue in their chosen specialties should they enter general practice. It will provide a stepping-stone from general practice to consulting work, which is now lacking. It will encourage some of those who intend to go into general practice to spend additional years in hospital after qualification, and to acquire postgraduate diplomas, thus helping to fill the vacancies in hospital junior medical staffs.

General-practitioner Beds in Hospitals

The report of the General Practice Review Committee of the British Medical Association said:

"It is part of the Association's hospital policy that beds in local hospitals should be available to general practitioners for the treatment by them of their own patients for conditions which are within the province of general practice." (*British Medical Journal* 1953c.)

The leading article in that issue of the *British Medical Journal* (1953b) said:

"The views expressed by the G.P. Review Committee, by Sir Heneage Ogilvie (1953), by Dr. Hamilton (1953) and by the Representative Body of the B.M.A. all point strongly to one greatly needed reform—the widespread provision of beds for general practitioners where they may give continuous care

to patients under their charge and in so doing, gain the satisfaction and instruction that come from responsible clinical work under good conditions."

That general practitioners, and especially general-practitioner specialists, should be able to treat some of their patients in hospital beds is just as important as for them to work in outpatient departments. Once again we must remind ourselves that a family doctor's first concern should be with his own patients, to supervise their comfort and their medical care, and to follow them up wherever they are. When they have to go to hospital because social factors prevent proper care in bed at home, with illnesses which do not need continuing consultant investigation or treatment, it is often right for their own family doctor to look after them. On an average, at present, each general practitioner in this country has rather less than a one-third share in one hospital bed! (Ministry of Health 1953).

Those in charge of general-practitioner beds in hospitals should treat not only minor disabilities. There are many major illnesses—pneumonia, cerebral thrombosis, cardiac failure, pyelitis, salpingitis, prolapsed lumbar discs, generalised carcinoma, and so on—during which a patient may wish to be looked after by his family doctor in bed in a hospital. The same principle applies also to many maternity cases. The more serious or hopeless a disease, the more often does a patient appreciate being looked after by someone he knows. Consultants should be attached to these hospitals and be invited to see many of these patients; they should take over into consultant beds, in their own wards, those who require continuing special investigation or treatment. With many patients, however, the routine work could well be done in a general-practitioner bed by the patient's family doctor, taking full responsibility himself, with consultant advice from time to time, and perhaps with a resident to help him in hospitals large enough to have a house-officer.

The revised Strachan report on Hospital Medical Staffing (para. 11) states:

"Another aspect of the problem is the almost complete breakdown of the old custom whereby a practitioner combined an appointment on the staff of his local hospital with a general practice. This has deprived the hospital service of a source of medical man-power which it can ill afford to lose." (*British Medical Journal* 1955.)

In the past, many general practitioners have done splendid work caring for their own patients in hospital beds; and even now, the breakdown in the old system is not everywhere quite as complete as the Strachan report suggests. There are 6525 general-practitioner beds for about 20,000 family doctors (Ministry of Health 1953). In the four Metropolitan regional areas there are 123 hospitals with general practitioners on their staffs, but in by no means all of them have family doctors charge of beds, and none are in Central London. *There is an urgent need to increase the number of general-practitioner beds—for country districts in general-practitioner hospitals, for urban districts in branches or annexes of general hospitals.*

The Strachan report recommends (para. 31) that the responsibility for the treatment of *all* hospital patients must remain in the hands of those of consultant status. This recommendation may not always be necessary or practicable. Consultants may not be able, or wish, to see every patient who is being treated in a general-practitioner bed, and it will be unwise for them to be held responsible for patients they never examine. It is doubtful whether general practitioners will be pleased for their beds to be supervised or controlled by consultants from a distance.

Research in General Practice

The growing-points of medicine touch on a great deal of a family doctor's work, and there is a potential contribution to knowledge to be made by general practitioners in a wide variety of subjects—in epidemiology; in the prevention, diagnosis, prognosis, or treatment of almost every illness; in the genetics of disorders in circumscribed or isolated communities; in studies of the natural history of illnesses which do not reach hospitals; in the planning and design of new equipment and premises; in the use of new materials (such as plastics and nylon); in testing new apparatus; in methods of record-keeping; in many administrative fields; and in certain aspects of special subjects such as industrial medicine, social medicine, public health, nursing, geriatrics, medical statistics and so on. There is no illness, administrative problem, or special subject with which some general practitioner may not have an unexpected or unusual experience which is worth following up, or with which he may not now be dealing in a way that is better than has been tried before. There is need to encourage and coördinate these experiments and to recognise those who are doing this work. Prof. J. M. Mackintosh (1955) and others (*Lancet* 1955) have recently discussed in detail how best this may be done.

The College of General Practitioners

This college, founded in 1952 (*British Medical Journal* 1952), is now firmly established in its attempt to improve the efficiency and good name of general practice; its help is being sought by many individuals and by many academic groups and organisations (*Practitioner* 1953, 1954). Some people suggested that its foundation was merely a symptom of general-practitioner discontent in Great Britain at that time. Rather should one say, now, that the American Academy of General Practice (with its 19,000 members), our own college, the College of General Practice of Canada and similar movements in Africa, Australia, and New Zealand are, each in its own way, symbols of a rejuvenation of general practice the world over which should bring nothing but good to the future of our profession.

Summary

There is need for further bold experiment in many matters concerning general practitioners, more especially in the development of departments of general practice in medical schools, in the trial of diagnostic and treatment centres as an alternative to health centres, in the work of family doctors in hospital outpatient departments, and in the provision of more general-practitioner hospital beds. Possible lines on which such experiments might be conducted are discussed.

With the overcrowding, at present, of hospital outpatient departments, and the shortage of junior medical staff, it is likely that more general practitioners will be asked before long to help in the work of hospitals. A possible place for the general-practitioner specialist in a team of specialists is described.

The needs of hospitals must be met, and practitioners will no doubt play their full part in this, but in doing so the equally urgent needs of the family doctor himself must not be overlooked. His first duty is to his *own* patients, for whom he alone is fundamentally responsible. It is just as important that he should be given all possible help and encouragement to diagnose and treat these efficiently himself, in their homes *and* in hospital, as it is to invite him to assist consultants in hospitals treating the patients of other doctors.

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INSENSITIVITY TO VITAMIN D DEVELOPING DURING THE TREATMENT OF POSTOPERATIVE TETANY

ITS SPECIFICITY AS REGARDS THE FORM OF VITAMIN D TAKEN

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THE treatment of choice for permanent postoperative hypoparathyroidism is oral vitamin D in one of its forms, and most workers who have written on the subject have been quite satisfied with their results (Holtz 1941, Albright and Reifenstein 1948, Stucki 1950).

It seems clear from the literature that there is little to choose between the various preparations used. 'A.T.10' (which we shall regard here as a form of vitamin D) and calciferol are those most commonly used. They appear to have identical actions, although A.T.10 exerts, and ceases to exert, its action rather more quickly, which therefore makes it a little easier to use in controlling treatment. A disadvantage in using A.T.10 is its much greater cost compared with calciferol. The dose of calciferol has been variously reported as 1–5 mg. (40,000–200,000 units) a day. The only other commonly available forms of vitamin D—namely, A.T.10 and vitamin D_3, appear to be active in a similar dose (weight basis) when given orally (Schultzer and Christensen 1946, Stucki 1950, Jesserer and Blacizek 1951). McLean (1941), however, stated that 2 mg. a day of calciferol is equivalent to 1 mg. of A.T.10. He was emphatic that patients do not develop tolerance to calciferol or A.T.10 on long-continued administration.

Some authors, however, have noted variations in tolerance to the vitamin, since they have remarked on the need to vary the dose from time to time. A case unusually resistant to therapy with both A.T.10 and calciferol has been described by Blohm et al. (1953), and occasional acquired insensitivity to either calciferol or A.T.10 has been discussed briefly by Howard and Connor (1954).

In the last few years we too have occasionally noticed that patients may become exceedingly insensitive to the action of calciferol. After they have responded well at first to normal doses we have had to increase the dose considerably, until perhaps they were having as much as 12 mg. a day without relieving the tetany. We found that this happened with calciferol given both in a proprietary form and as the pure substance mixed only with lactose.

While these difficulties were being experienced in patients with postoperative tetany, we encountered a similar phenomenon in the metabolic ward, where patients were being treated with large doses of calciferol for various metabolic forms of rickets and osteomalacia. In these cases, however, there seemed to be an increasing insensitivity to the antirachitic and other metabolic effects of the vitamin. We wondered how specific this reaction might be, and noted that such patients who had become insensitive to calciferol might be normally sensitive still to A.T.10, whether crude or as pure crystalline dihydrotachysterol. These particular researches are being continued and will be published later in more detail. They led to the investigations on patients with postoperative tetany, and we are reporting these now because they involve a simpler problem with a more immediate practical application.

Methods

Calcium was determined by permanganate titration of the precipitated oxalate, in plasma by the method of Clark and Collip (1925), in urine by that of Shohl and Pedley (1922). Plasma-phosphorus was determined by the method of Fiske and Subbarow (1925). Creatinine in urine was determined by alkaline picrate according to the method of Folin (1914).

The calcium balance studies were all done in our metabolic ward using the general principles laid down by Reifenstein et al. (1945). The patients were given a diet which was maintained unaltered throughout the period of the balance study but was, in the first instance, composed so as to accord with their own preferences and with our requirement of mineral intake. After six days for equilibration, collections of urine and stools were begun. Carmine markers were used, the stools being bulked and analysed in six-day periods. A complete day's diet was analysed several times during each balance study.

All blood samples for chemical analysis were taken at 9 A.M. with the patient fasting (breakfast being delayed)

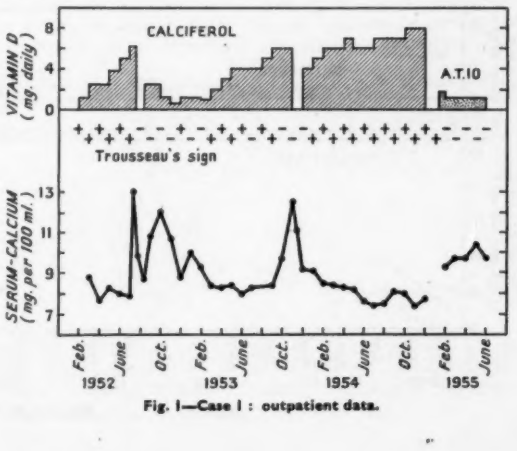

Fig. 1—Case 1 : outpatient data.

* In receipt of a grant from the Sir Halley Stewart Fund.

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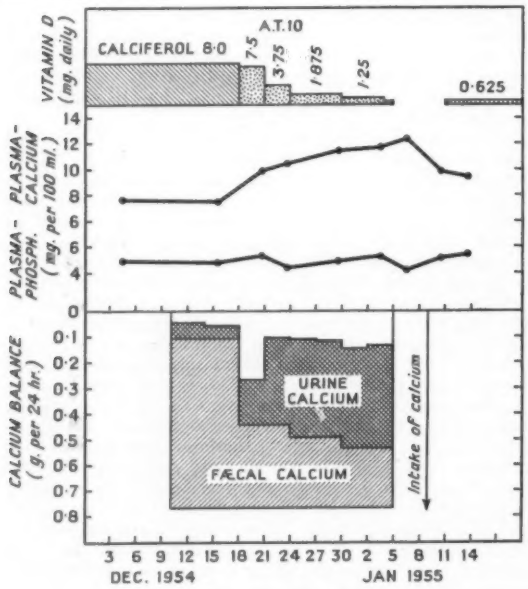

Fig. 2—Case 1 : metabolic data.

so as to standardise diurnal and other causes of variation. The blood was heparinised and quickly centrifuged, and the plasma was used for analysis. Hæmolysed specimens were rejected.

Determinations of urine creatinine were used as a check on accuracy of urine collection. The results will not be given here.

The vitamin-D compounds were given (unless otherwise stated) as pure calciferol (ergocalciferol, vitamin D_2) or pure vitamin D_3 (cholecalciferol, natural vitamin D), or as A.T.10 solutions in oil (1 capsule or 0·5 ml. being equivalent to 0·625 mg. of pure dihydrotachysterol). A.T.10 is a crude preparation from irradiated ergosterol, biologically standardised. It was obtained from Farbenfabriken Bayer, Leverkusen.

Case-reports

Case 1.—A woman, now aged 39, was first seen in February, 1952. In December, 1950, she had undergone subtotal thyroidectomy at another hospital. Symptoms of tetany had started on the day after the operation. She was treated with calciferol and, when we saw her, was taking 1·2 mg. on alternate days. During this period her serum-calcium level was 8·2–10·0 mg. per 100 ml., and she appears to have been free from symptoms. However, when we first saw her, she gave a strongly positive Trousseau's sign, and the dose was increased to 1·2 mg. daily.

Her subsequent progress is shown in fig. 1. A bout of hypercalcæmia, with thirst and vomiting, came on unexpectedly in July, 1952, the dose at that time having been raised to 6 mg. The same symptoms recurred with hypercalcæmia in October, 1952, and November, 1953. After the last of these bouts she remained resistant to calciferol and was admitted to the metabolic ward in December, 1954.

Treatment and Progress.—On admission she was maintained at first on her previous dose of calciferol 8 mg. a day, and control biochemical determinations were undertaken. During this time she continued to have signs and symptoms of tetany. On Dec. 18, 1954, she was given A.T.10 7·5 mg. a day instead of the calciferol. Next day she suddenly became aware that her symptoms had disappeared, and we noted that Trousseau's and Chvostek's signs were now negative. Her A.T.10 dose was gradually reduced in the next four days but not quickly enough to prevent a few symptoms of hypercalcæmia. The metabolic data are summarised in fig. 2.

Follow-up.—As an outpatient she has been satisfactorily maintained on small doses of A.T.10 (fig. 1).

Case 2.—A woman, now aged 68, underwent partial thyroidectomy in 1924 for what was probably a toxic goitre. The goitre recurred in 1946, and a second thyroidectomy was performed in April of that year. Tetany developed five days after the operation. She was treated with intravenous calcium gluconate and calciferol by mouth. The calciferol appears to have been continued, but the dosage is uncertain until November, 1946.

The patient's progress from then on is shown in fig. 3, which shows that, after a period of apparent insensitivity to calciferol in doses of up to 5 mg., hypercalcæmia suddenly developed in August, 1953, accompanied by thirst and vomiting. After this episode she was again apparently insensitive to calciferol, except for a brief period in November and December, 1953. In March, 1955, she was admitted to the metabolic ward.

Treatment and Progress.—On admission she was maintained at first on her previous dose of 8 mg. of calciferol a day, and control biochemical determinations were undertaken. During this time she continued to have signs and symptoms of tetany. On April 13, 1955, her calciferol was stopped, and she was given instead the same weight (8 mg.) of vitamin D_3. In the next two or three days she lost her symptoms of tetany and felt much better. Chvostek's sign, however, remained positive for a week or two. On April 28 she reported unusual feelings of depression, which we interpreted as due to impending intoxication, especially as by then her urinary output of calcium had increased considerably. Her dosage of vitamin D_3 was therefore reduced to 2 mg. a day, and she soon felt entirely well and was sent home on this dose on May 10. Her metabolic data are summarised in fig. 4.

Her *follow-up* is shown in fig. 3.

Case 3.—A woman, now aged 70, was first seen in 1953. In 1940 she had undergone partial thyroidectomy at another hospital. Two months later she became bloated, and her hair fell out, and treatment with thyroid extract was started. She did not spontaneously complain of cramps, but Trousseau's

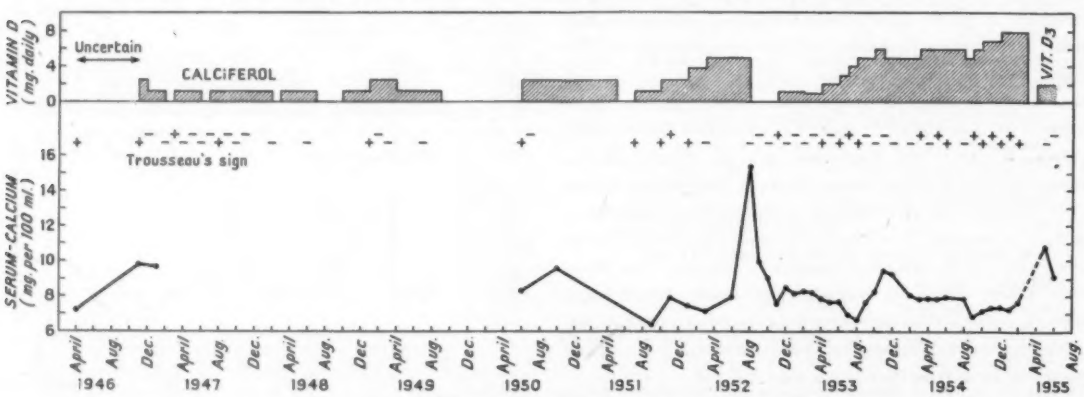

Fig. 3—Case 2 : outpatient data.

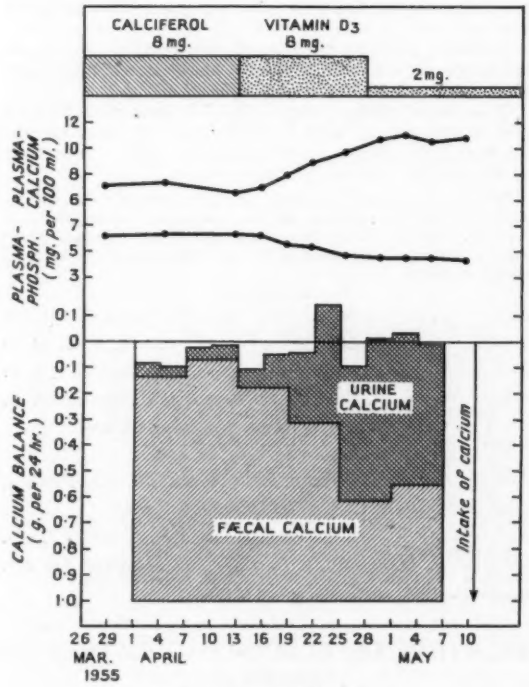
CALCIFEROL 8 mg.
VITAMIN D3 8 mg.
2 mg.
PLASMA-CALCIUM (mg. per 100 ml.)
PLASMA-PHOSPH.
CALCIUM BALANCE (g. per 24 hr.)
URINE CALCIUM
FÆCAL CALCIUM
Intake of calcium
26 29 1 4 7 10 13 16 19 22 25 28 1 4 7 10
MAR. APRIL MAY
1955

Fig. 4—Case 2 : metabolic data.

sign was strongly positive, and her serum-calcium level was 7·45 mg. per 100 ml.

Treatment and Progress.—Treatment with calciferol was started, and she was also given sodium L-thyroxine 0·1 mg. daily, this dose being maintained unchanged throughout the period of observation. Her subsequent progress is shown in fig. 5. An episode of hypercalcæmia occurred in November, 1953, accompanied by thirst. By March, 1955, she seemed to have become resistant to calciferol even on the dose which had previously intoxicated her. A.T.10 was accordingly substituted, and she was immediately sensitive to a much smaller dosage.

Case 4.—A woman, now aged 46, underwent partial thyroidectomy for thyrotoxicosis in 1933. Enlargement and overactivity of the thyroid recurred in 1938, and a second partial thyroidectomy was performed. The symptoms recurred again in 1942, when further thyroid tissue was removed. Since then the patient has remained euthyroid. Tetany was noticed eight days after the third operation, the serum-calcium level being 6·8 mg. per 100 ml.

Treatment and Progress.—She was treated for two weeks with intravenous calcium gluconate, parathyroid extract ('Parathormone'), and calciferol. Tetany was rapidly abolished, and she afterwards remained symptom-free while taking calciferol alone. Her subsequent progress is shown in fig. 6. An episode of hypercalcæmia developed in July, 1952, accompanied by malaise and vomiting. From January, 1954, onwards she became relatively resistant, but the symptoms of tetany did not worry her unduly. However, when A.T.10 was substituted for calciferol in April, 1955, the signs of tetany disappeared and she said she felt better than she had done for several years.

All four patients at one time or another showed sudden striking increases in sensitivity to calciferol—usually sufficient, indeed, to cause signs and symptoms of intoxication. Curiously enough, these appeared to coincide in time. All the three patients taking calciferol in July and August, 1952, developed hypercalcæmia (figs. 1, 3, and 5); and of the three patients taking calciferol in November, 1953, one developed hypercalcæmia (fig. 1), while the remaining two showed a sharp rise in blood-calcium level (figs. 3 and 6). We cannot explain these events: they did not seem to be related to a change in the source or batch number of the preparation used.

Discussion

We have described four cases in which, after accidental surgical removal of their parathyroid glands during operations on the thyroid gland, the patient had chronic hypocalcæmic tetany. All showed a greatly increasing insensitivity to the hypercalcæmic action of calciferol, even though the patient had been symptom-free and normocalcæmic before on smaller doses. When the same smaller doses of A.T.10 (three cases) or of vitamin D_3 (one case) were substituted for the calciferol, the symptoms of tetany were rapidly relieved, and the plasma-calcium level rose to normal. All four patients are now well maintained on relatively small doses of the substituted substances.

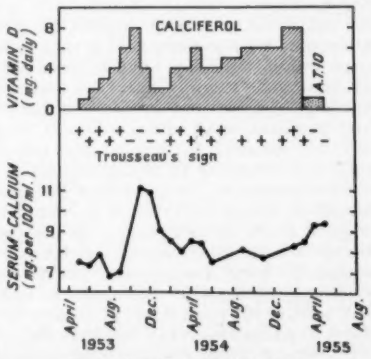

Fig. 5—Case 3 : outpatient data.

The calcium balance and other data obtained in cases 1 and 2 at the time of the change of the vitamin-D preparation showed that both patients in the phase of insensitivity to vitamin D appeared to show no response at all to the action of their large dose of calciferol. They had poor absorption of calcium from the gut and a low urinary excretion of calcium besides having low plasma-calcium and raised plasma-phosphorus levels. It thus appeared that the calciferol had ceased to exert any appreciable effect on their metabolism. However, as soon as the form of administered vitamin D was changed, all the actions of vitamin D were immediately manifest—namely, improved absorption of calcium from the gut, decreased renal threshold for calcium, raised plasma-

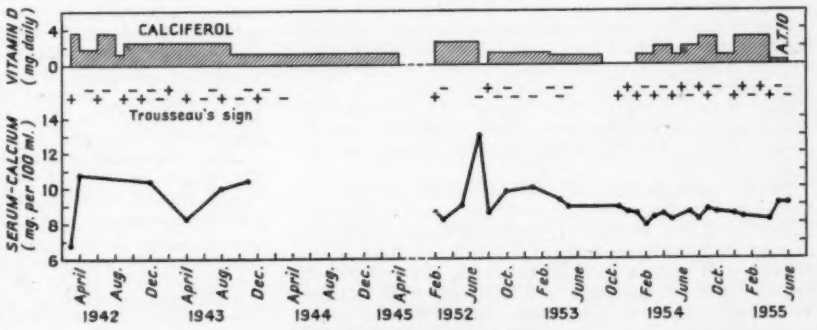
CALCIFEROL
A.T.10
VITAMIN D (mg daily)
Trousseau's sign
SERUM-CALCIUM (mg. per 100 ml.)
April Aug. Dec. April Aug. Dec. April Aug. Dec. April Feb. June Oct. Feb. June Oct. Feb June Oct. Feb. June
1942 1943 1944 1945 1952 1953 1954 1955

Fig. 6—Case 4 : outpatient data.

calcium levels, and (in one of the two cases) a fall in the plasma-phosphorus level. A further action of vitamin D can also be implied from the timing of the rise in plasma-calcium level. In both cases this rise preceded changes in calcium absorption sufficient in themselves to produce such rises. These were offset by the approximately equal rise in urinary calcium; hence the over-all calcium balance remained unchanged. It seems clear that this was due to the direct action of the vitamin D on bone.

All our evidence suggests, therefore, that the patients who had been previously sensitive to calciferol in small doses had become completely insensitive to it even in large doses, but that this insensitivity at that time was to calciferol alone and not to normal doses of the closely related substances A.T.10 and vitamin D_3.

To this factual matter we can add a few words which illustrate our present view. This is based on evidence not yet convincing enough to be published in proper form, as well as on evidence already in the literature.

We suspect now that insensitivity to vitamin D is likely to develop in any patient given large doses of vitamin D. We think this may happen with any of the preparations of vitamin D, and that, as shown here only for calciferol, it will be specific for the preparation in question. We also think that in each case the insensitivity may disappear many months after the particular form of vitamin-D therapy has been discontinued. We thus envisage a treatment of postoperative tetany in which any preparation of vitamin D will be used at first but will be replaced by one of the other preparations if insensitivity seems to be impending.

The theoretical implications of this rather curious situation, which we think is unique as regards vitamins, require much further study. We are also studying the occurrence or otherwise of insensitivity in our cases of metabolic bone disease—e.g., steatorrhœa, renal osteodystrophy, idiopathic osteomalacia, and resistant rickets—treated with large doses of a form of vitamin D. We hope to publish soon the fact that they, too, often benefit by a change from one preparation to another. It now looks as though some cases of resistant rickets and osteomalacia respond at first to relatively small doses of vitamin D but very rapidly develop a very severe insensitivity to its various metabolic effects. Perhaps, therefore, this phenomenon, which in many cases appears to be determined by genetic factors, is similar in kind to, but different in degree from, the more slowly acquired insensitivity described here in our patients with tetany.

The opposite situation of oversensitivity to vitamin D also appears to develop in some patients with sarcoidosis (Anderson et al. 1954) and perhaps also in infants with "idiopathic hypercalcæmia of infancy with failure to thrive" (Bonham Carter, Dent, Fowler, and Harper 1955). It may be necessary to explore the possibility that this state of oversensitivity may involve only one or other preparation of vitamin D.

Summary

Some patients with postoperative tetany, when taking a dose of calciferol that has been sufficient to maintain their plasma-calcium levels, may for no apparent reason become insensitive to this dose and remain insensitive even when the dosage is greatly increased.

Two patients taking large doses of calciferol were closely studied while they were in the calciferol-insensitive phase. None of the metabolic actions of calciferol was manifest.

In four patients who had become calciferol-insensitive a change from large doses of calciferol to normal doses of A.T.10 or of pure vitamin D_3 produced a rapid disappearance of the tetany and a return to normal of their plasma-calcium and plasma-phosphorus levels. In two patients the change from calciferol to A.T.10 and from calciferol to vitamin D_3 was undertaken under full metabolic control. This showed that the change of vitamin-D preparation coincided with the onset of normal vitamin-D action.

It seems probable that the future treatment of postoperative tetany will comprise changes, as necessary, from one form of vitamin D to another.

This curious phenomenon is likely to have some bearing also on the pathogenesis and treatment of those various forms of bone disease which include so-called "resistance to vitamin D" as one of their features.

We wish to thank Sister K. Buck for nursing care of the patients and supervision of the metabolic arrangements; Mrs. B. Dewing, who supervised the preparation of their diets; and Prof. M. Maizels for the outpatient biochemical determinations.

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RELATION OF BLOOD-COAGULATION TO LIPÆMIA

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AN impressive volume of evidence, recently summarised (*British Medical Journal* 1954), suggests that the ingestion of fat may increase the liability to thrombosis. Macfarlane et al. (1941) showed that lipoids may play an important part in in-vitro blood-coagulation, and Fullerton et al. (1953) and Vandenbroucke et al. (1954) that after a large fatty meal the clotting-time is significantly shortened.

I report here some of the effects on clotting of giving healthy volunteers a standard breakfast containing various quantities of fat. I also tried to find whether particulate fat (chylomicra) or soluble fat was primarily responsible for the changes observed.

First Experiment

Methods

The volunteers were healthy working men and women between the ages of 20 and 52. All of them were asked to fast after 8 P.M. on the preceding day. The first fasting sample of blood was taken into a siliconed syringe. Twenty minutes later a second fasting sample was taken. The volunteers then ate the breakfast, which contained 50 g. of animal fat. Two further samples, called lipæmic samples, were taken twenty minutes apart about the end of the fourth hour, when the lipæmia was usually at its peak.

Coagulation tests were made on each of the four samples. The results of the first two samples were averaged and called fasting clotting-times, and those of the second two were averaged and called lipæmic clotting-times.

Four small silicone-coated (D.C.1107) test-tubes already warmed to 37°C were each filled immediately after the venepuncture with 1 ml. of blood from the syringe, and the "silicone clotting-time" of each was recorded.

In the case of some of the volunteers a further three non-siliconed tubes containing a knife-point of powdered glass

TABLE I—RESULTS OF FIRST EXPERIMENT

Sex	Age (yr.)	Blood: Silicone clotting-time (min.) F	Blood: Silicone clotting-time (min.) L	Platelet-poor plasma: Clotting-time (min.) F	Clotting-time (min.) L	T.G.T. (min.) F	T.G.T. (min.) L	Fibrinogen F	Fibrinogen L	Fat: Total F	Total L	Non-particulate increase	Chylomicra increase
M	38	17	16½	7·20	4·43	11¾	11½	2·28	2·00	325	417	34	58
M	38	20¼	19½	9·45	9·30	13½	13¼	1·54	2·23	370	405	0	35
F	23	19½	16	6·47	5·16	13	11	1·55	2·32	275	290	..	..
F	23	22	16½	7·32	6·38	12½	10¼	2·29	1·53	276	333	48	9
F	33	17	15	5·53	3·31	12¼	12¼	2·39	1·28	319	440	45	76
F	33	19½	17¼	9·50	7·22	12¼	10¼	2·48	1·55	335	401	..	..
F	33	19	22¾	6·38	3·11	11¼	7¾	1·30	1·08	406	468	44	18
F	35	18¼	16	8·13	6·45	11¾	12	2·21	2·02	254	400	..	..
F	35	19	18	6·45	5·45	12¾	11	2·07	1·20	300	430	90	40
F	28	18	16	7·20	5·50	14½	12¼	2·09	2·04	206	250	21	23
M	52	16	20	6·38	5·05	12	10½	2·33	2·10	470	676	..	..
M	52	31½	21½	4·15	3·52	10	10¼	1·34	1·05	495	690	202	–7*
M	52	17½	14	5·30	5·15	10½	10¼	1·27	1·52	370	497	89	91
M	48	20	15	7·23	6·15	13¾	11½	2·16	2·47	390	470	41	39
M	45	18	13½	8·11	6·56	13½	14¼	1·44	1·28	..	..	..	..
M	45	21	19	6·04	3·40	12	9½	2·12	1·07	345	345	–58	58†
M	48	17½	18	8·00	4·51	14½	10	2·29	1·10	270	480	167	43
M	38	26	23	9·53	7·30	14½	12½	1·35	1·52	397	596	18	171
F	20	27½	24½	7·11	9·38	11¼	13¾	2·11	2·15	300	316	0	16
M	35	20½	19¾	7·23	5·26	12	10	2·03	1·21	340	435	90	5

*Fasting plasma repeatedly contained chylomicra: fasting total fat 495, lipæmic total fat 690, fasting chylomicra fat 61, lipæmic chylomicra fat 54.
†There was apparently a decrease in non-particulate fat after the meal.
Chylomicra increase, that proportion (mg. per 100 ml.) of the lipæmic increase removable by seitz-filtration—i.e., particulate fat.
F, fasting.
L, lipæmic.
Non-particulate increase, increase (mg. per 100 ml. of plasma) of non-particulate ether-extractable plasma-lipoids 4 hr. after the meal.
T.G.T., thrombin generation-time (minutes).

were next filled with 1 ml. of blood, and the clotting-times were recorded.

4·0 ml. of the blood was mixed with 0·4 ml. of isotonic citrate solution and centrifuged at 1000 r.p.m. for seven minutes. The supernatant fluid is called platelet-rich plasma, on which duplicate thrombin-generation tests were made. To 0·4 ml. of warmed plasma 0·4 ml. of M/40 calcium chloride was added, and the plasma clotting-time of this reacting mixture was recorded. Thereafter, at intervals, 0·1 ml. from the reacting tube was transferred to a subsample tube containing 0·4 ml. of a 2·0% solution of fibrinogen. The shortest clotting-time in any of these subsamples is called the fibrinogen time, and the interval between the recalcification of the plasma and the filling of the fibrinogen-time subsample tube will be called the thrombin-generation time. The reported results are the average of the 4 estimations (2 from each of the two samples, either fasting or lipæmic).

Platelet-poor plasma was obtained by centrifuging another 4 ml. of citrated blood at 3000 r.p.m. for fifteen minutes. Each sample of supernatant plasma was tested in duplicate by a similar thrombin-generation test.

Estimation of plasma fat.—The rest of the blood from the venepuncture was transferred to a tube containing solid potassium oxalate.

The oxalated blood was centrifuged at 3000 r.p.m. for fifteen minutes, and its optical density was measured at once in a 'Unicam' spectrophotometer at 1000 Å.

Fat was estimated by a modification of the fæcal-fat method of Van de Kamer et al. (1949). The plasma was saponified and then hydrolysed. The fatty acids were extracted with petroleum ether and eventually dissolved in 95% ethyl alcohol and titrated with sodium hydroxide. The two clear fasting-plasma samples were mixed, and the fat was estimated; the total lipoids in the lipæmic plasma were similarly estimated.

Another moiety of the pooled opaque lipæmic plasma was seitz-filtered. This produced a completely clear plasma, which I call chylomicra-poor plasma. The fat-content of this was estimated. Some samples were centrifuged at 9000 r.p.m. for 120 minutes; this also produced a clear plasma, and the fat was estimated. The difference between the total fat in the lipæmic plasma and the estimable fat after seitz-filtration was assumed to be due to fat in the form of particulate fat or chylomicra. The increased amount of fat in the seitz-filtered lipæmic plasma above the fasting-fat level was assumed to be due to an increase in the non-particulate or soluble fat.

Results

Preliminary.—Preliminary observations showed that, in the absence of ingestion of fat, there were no significant changes in the blood lipoids or in the clotting-times; so it seems likely that the ingestion of fat is in some way responsible for any changes found after a fatty meal.

The fasting platelet-poor plasma was nearly always practically clear, and seitz-filtration did not cause a decrease in the estimable fat; so these observations were not continued for the whole series. The clotting-times in the presence of powdered glass and the thrombin-generation results of platelet-rich plasma in the first 11 cases showed no appreciable changes after the meal, compared with the fasting results; so these observations were not continued. The fat-content of the seitz-filtered plasma and that of the plasma centrifuged at high speed were the same; so the estimation of centrifuged samples was discontinued. The possibility remains that both methods did not in fact remove all the particulate fat.

Coagulation.—The main series comprised 20 investigations on thirteen volunteers and is presented in table I. Not all the investigations were made in every experiment, and those made show considerable variation. However, the lipæmic silicone clotting-times were usually shorter than the fasting silicone clotting-times, and for the whole series the difference was significant at a 0·1% level of confidence. The difference between the lipæmic and starved plasma as regards thrombin-generation times was significant at a 5·0% level of confidence, and as regards fibrinogen at a 1·0% level. The statistical test used was Fisher's (1935) modification of Student's (1908) t test.

Lipæmia

There was considerable variation between individuals both in the fasting blood-fat level, which was fairly constant for each individual, and in the postcibal increase, which was variously distributed between non-particulate and particulate fat. There was no relation between the opacity measurements and any of the estimations of plasma-fat.

Relation of coagulation to lipæmia.—To compare the changes in the clotting-times with the changes in the fat-content the difference between the shorter lipæmic clotting-time and the fasting clotting-time was expressed as a percentage of the fasting clotting-time; this enabled the degree of change in all the four clotting-times (silicone

clotting-time, plasma clotting-time, thrombin-generation time, and fibrinogen time) to be averaged to present an over-all average estimate of the acceleration of the clotting mechanism.

If the observed postcibal acceleration of the clotting-times is related to the lipæmia, it should probably be possible to show some proportionality between some or all (using the over-all average) of the percentage acceleration of the clotting-times and the percentage increase in the total, or the particulate or the soluble fat, or in the opacity in each case. All these possibilities were investigated, and none showed any significant correlation.

Second Experiment

A further attempt was made to see if the postcibal acceleration of clotting was proportional to either or both the particulate or non-particulate plasma-fat.

Method

Four healthy male or female volunteers aged 55–70 were used. Two samples of blood were taken immediately before breakfast. The meal consisted of 60 g. of animal fat. Blood was collected 1, 2, 3, and 4½ hours after the meal. Thrombin-generation tests were made on some samples. 'Stypven' times were estimated on all the samples as follows:

To 0·1 ml. of warmed plasma was added 0·1 ml. of stypven (Russell's-viper venom). Immediately after, 0·1 ml. of calcium chloride was added, and the clotting-time was recorded. The average of two or more observations was taken as the stypven time.

The total ether-extractable lipoids before and after seitz-filtration were estimated on all samples.

Results

An acceleration of clotting-times and an increase in particulate and non-particulate lipoid were usually observed. In no case did the increase in the lipoid, particulate, or non-particulate, vary even approximately in proportion to the acceleration of various clotting-times. Indeed in several one-hour periods there was a considerable change in these two measurements, but in opposite directions—e.g., an increase in both forms of fat and a lengthening of the clotting-times. Again it must be concluded that there is no direct relation between the total increase in particulate or non-particulate ether-extractable plasma-lipoid and the acceleration of the clotting-times.

Third Experiment

The absence of a quantitative correlation between the changes in plasma-fat and the changes in coagulation does not necessarily imply that chylomicra play no part in the acceleration of coagulation. The following experiment was designed to investigate further their activity. The clotting-times of fasting and lipæmic platelet-poor plasma were compared with similar observations on the same two plasmas largely freed from chylomicra. Lastly, chylomicra were added back to the sample of chylomicra-poor plasma, enabling a direct comparison to be made between chylomicra-rich and chylomicra-poor plasma.

Method

Two venepunctures were made on the fasting volunteer, who then ate as much animal fat for breakfast as possible. This was usually about 70 g. About three and a half hours later two further venepunctures were made. Each of these 4 samples was treated identically. Each sample was centrifuged at 3000 r.p.m. for twenty minutes to produce platelet-poor plasma. Some of this plasma was used in the coagulation tests. The rest was divided equally between two centrifuge tubes, which were centrifuged at 9000 r.p.m. for two hours. This produced a small deposit with clear supernatant plasma and a scum of chylomicra on the surface. From one tube some of the clear plasma was carefully removed with minimal disturbance of the scum, this is the "chylomicra-poor plasma." The plasma and fat scum of the second tube were mixed and poured into another tube, leaving the deposit, if any, in the centrifuge tube. This last plasma sample thus contained resuspended chylomicra and is called chylomicra-rich plasma. The coagulation tests, made in duplicate on each sample, were the thrombin-generation test described above and a stypven time.

TABLE II—RESULTS OF THIRD EXPERIMENT

—	T.E.		F.T.		Stypven	
	Fasting	Lipæmic	Fasting	Lipæmic	Fasting	Lipæmic
Platelet-poor plasma ..	12·0	12·0	94	70	25·0	18·0
% acceleration	0		25		28	
Chylomicra-poor plasma..	12·7	11·6	165	143	27·7	20·9
% acceleration	9		19		25	
Chylomicra-rich plasma..	12·6	11·6	155	126	27·3	20·6
% acceleration	8		19		28	

F.T., average shortest clotting-time (sec.) of any of fibrinogen subsample tubes.
Stypven, average stypven time (sec.).
T.E., average time elapsed (minutes) between addition of calcium to reacting mixture and taking of shortest subsample.

Results

The average figures from seven volunteers are presented in table II. Several comparisons can be made. First it will be seen that the degree of change (% acceleration) of the stypven times gave results very similar to the degree of change in the fibrinogen times, suggesting that under these conditions the stypven time was measuring the same phenomenon as the fibrinogen times. This contention was supported by a similar close proportionality in each case.

A comparison of the results obtained with platelet-poor plasma and those obtained with chylomicra-poor plasma shows that the degree of difference between the fasting and the postcibal samples is not altered by these two different treatments of the plasma; nor is this difference removed by adding back an excess of chylomicra in the chylomicra-rich samples. It can probably be concluded that most of the chylomicra play little part in the difference in coagulation between the fasting and the postcibal samples of plasma.

However, high-speed centrifuging to produce chylomicra-poor plasma did lengthen all the clotting-times. This was probably partly, but not necessarily wholly, explained by a more complete removal of platelets, since the minute deposit was shown to be highly active, and platelets are known to improve the performance of the thrombin-generation test and the stypven time.

The adding back of excess chylomicra slightly shortened the clotting-times, which fact is of doubtful significance. Poole (1955) has shown that the clotting of rat plasma, freed from chylomicra by very-high-speed centrifugation, can be greatly accelerated by the addition of washed rat chyle—i.e., chylomicra free from platelets. Poole concluded that chylomicra can play an active part in blood-coagulation, whereas my results so far do not show that, under the given experimental conditions, they play any part. These apparently discrepant resulks may be explained if centrifuging human plasma at about 9000 r.p.m. does not free plasma completely from all chylomicra, and if the activity of chylomicra depends on the presence of only small numbers of chylomicra. It should be repeated that a very large proportion of the particulate fat was in fact removed; there was no difference in the fat-content of lipæmic plasma rendered chylomicra-poor by high-speed centrifugation and by seitz-filtration and the plasma was in both cases optically completely clear.

An attempt was made to prove these suggestions. Various kinds of platelet-poor plasma were centrifuged

in a cooled centrifuge at 20,000 r.p.m. for up to two hours, and some of the plasma was removed through the side of the plastic centrifuge tube, so that no contamination with the supernatant chylomicra was possible. The scum of chylomicra was then mixed with a small amount of the plasma. These two plasmas and the untreated plasma were compared by the stypven-accelerated clotting-times, and gave the following results, which are the averages of eight experiments:

Untreated	*Chylomicra-poor*	*Chylomicra-rich*
16·1 sec.	23·8 sec.	16·7 sec.

These findings are in agreement with Poole's observations on rats, and indicate that, if the chylomicra are sufficiently thoroughly removed, the stypven time is lengthened and can be restored to normal by the addition of chylomicra. The results from this very-high-speed centrifuging were inexplicably erratic, and it was felt that an extended series was unlikely to give more information.

It seems that the more complete the removal of chylomicra the more emphatic is their effect on being added back to plasma. Since there is no quantitative relation between the quantity of fat as chylomicra and the acceleration of the postcibal clotting-time, and since this acceleration persists in spite of the removal of most of the chylomicra, it seems unlikely that the chylomicra are solely responsible for the acceleration of coagulation after a fatty meal.

Conclusions and Summary

In the presence of platelets and a water-wettable surface there is no detectable difference in the clotting-time of lipæmic blood after a meal of 50 g. of fat compared with that from the same patient starving. When the platelets are largely removed or unable to act (silicone tubes), lipæmic blood clots faster than the equivalent fasting sample, and apparently more thrombin is generated. Gross variations were observed between individuals in the fasting blood-fat level and in the postcibal increase in particulate and non-particulate fat, but the behaviour of each individual was fairly constant. The acceleration of the clotting-time shows no significant proportionality to the increase in particulate or non-particulate fat. In the second experiment, when all the changes were studied hourly after a large fatty meal, no direct relationship was shown between the increase in total particulate or non-particulate fat and the acceleration of the clotting-times. In these circumstances the changes in the one-stage stypven times seem to vary directly in proportion to the fibrinogen times of the thrombin-generation tests.

In the third experiment most of the chylomicra were removed and, although all the times were prolonged by this procedure, the degree of postcibal acceleration of the clotting-times was unaffected. With even faster centrifugation, when the chylomicra were presumably more completely removed, the stypven time was prolonged and could be returned to normal by the addition of the chylomicra scum.

Possibly, had we been able to devise a reproducible method for removing all the chylomicra, we might have found that the postcibal acceleration of clotting was abolished, which would indicate that the chylomicra were responsible for the postcibal acceleration; but on the evidence available this seems unlikely. At least two possibilities remain. The observed acceleration may be due to a fraction of the ether-extractable lipoids, small in quantity but highly active, which does not increase in proportion to the total lipoids. Alternatively, the ingestion of fat may bring into play some independent mechanism; for example, it is conceivable that the heparin-like clearing activity (Jeffries 1954) incidentally affects the clotting mechanism.

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PENICILLIN IN MEGALOBLASTIC ANÆMIAS OF AFRICANS

EFFECT ON SERUM-VITAMIN B_{12} LEVELS AND ABSORPTION OF RADIOACTIVE VITAMIN B_{12}

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THE non-pernicious megaloblastic anæmias of Africans can be classified according to their response to treatment (Foy et al. 1951, 1952a, b, and c, Foy and Kondi 1953a and b). One group responds to 200,000 units of penicillin by mouth, or 400,000 units by intramuscular injection, daily for 6–12 days, or to a single dose of 80 μg. of vitamin B_{12} by mouth. The other group does not respond at all to penicillin or to 80 μg. of vitamin B_{12} (either oral or intramuscular), but does respond to oral folic acid 5–10 mg. daily for 5–10 days.

We have suggested that the responses to penicillin are probably due to (1) changes in the intestinal flora by which more vitamin B_{12} becomes available to the host, (2) intestinal changes favouring absorption, or (3) metabolic changes in the host leading to better utilisation of hæmopoietic substances.

We have now determined the serum-vitamin B_{12} levels, and the excretiop of radioactive vitamin B_{12} labelled with ^{60}Co, in both these groups of cases before, during, and up to four weeks after the start of penicillin treatment.

Of the cases studied, all those that responded to penicillin had very low serum-B_{12} levels which rose after the administration of penicillin, whereas those responding to folic acid but not to penicillin had serum-B_{12} levels ranging from normal to very high. Cases with serum-B_{12} levels below 700 μμg. per ml. showed some increase in these levels after penicillin, but this was not associated with any increase in red cells or hæmoglobin, although sometimes the reticulocytes increased slightly. Cases with serum-B_{12} levels above 700 μμg. per ml. showed no rise after treatment with penicillin, and no increase in reticulocytes, red cells, or hæmoglobin. The excretion of radioactive vitamin B_{12} was of the normal pattern in all patients, indicating that intrinsic factor was present. These results are, we think, in conformity with the view that changes in the intestinal flora are the important factor in the response to penicillin, but it is too early to decide whether this is the only factor.

We also estimated the serum-B_{12} levels in non-megaloblastic microcytic iron-responding anæmias of Africans and found that they ranged from normal to high.

Material

The cases were typical megaloblastic anæmias, such as we have previously described in Africans, with red-cell counts of 600,000–2,000,000 per c.mm., and reticulocytes about 1% on admission to hospital. The hæmatological examinations were made by the methods previously described (Foy et al. 1952b) and will not be dealt with in detail here. All the patients (except one with pernicious anæmia) had either normal gastric acidity or hypochlorhydria after the administration of intramuscular histamine 1 mg., and none had gastric atrophy, glossitis, or nervous symptoms. No patient had any evidence of sprue, and the fat-analysis was normal. The heart and lungs showed nothing incompatible with the extreme anæmia. No patient had malaria parasites in the blood or gave any recent history of malaria, but the spleen was enlarged in one. The stools contained no pathogens or parasites. A few of the patients had œdema of the ankles and/or eyelids; none had positive Wassermann or Kahn reactions. Three patients had watery diarrhœa, which, however, cleared up with the anti-anæmia treatment, no sulphonamides being necessary. The bone-marrow was active and contained either typical megaloblasts or the intermediate forms and giant stab-cells such as we have previously described.

The cases were kept under observation 3–10 days before the commencement of any treatment. Previous experience in a large number of cases, as well as experience in the cases we report below, indicates that hospital diet and rest in bed have no effect whatever on the hæmatological picture of these anæmias: patients remaining in hospital without treatment always show a decrease in the amount of hæmoglobin and in the numbers of red cells, and reticulocytes.

Treatment with the appropriate substances was followed in all cases by the maximal expected reticulocytosis, regeneration of the blood, and a return of the marrow to its normal picture.

Methods

Serum-B_{12} levels.—The serum-B_{12} was estimated using *Euglena gracilis* with the technique of Ross (1952), who kindly cross-checked some of our estimations. The values given for the various periods are the means of several estimations made at intervals of hours or days to exclude the effect of substances that promote the growth of euglena but are hæmopoietically inactive (Ross et al. 1954).

Excretion of radioactive vitamin B_{12} was estimated by a modification of the methods of Heinle et al. (1952), Halsted et al. (1954), and Callender et al. (1954). Radioactive vitamin B_{12} 0·5 μg., having an activity of 0·187 μC, was taken up in 100 ml. of water and given to the fasting patient at 10 A.M. Complete stools were collected daily until no further radioactivity was present. If the patients were constipated, cascara was given. Radioactivity was measured with a scintillation counter and checked for us either by Dr. S. T. Baker, of the Postgraduate Medical School of London, or by Dr. J. Loutit and Dr. F. Harrison at Harwell.

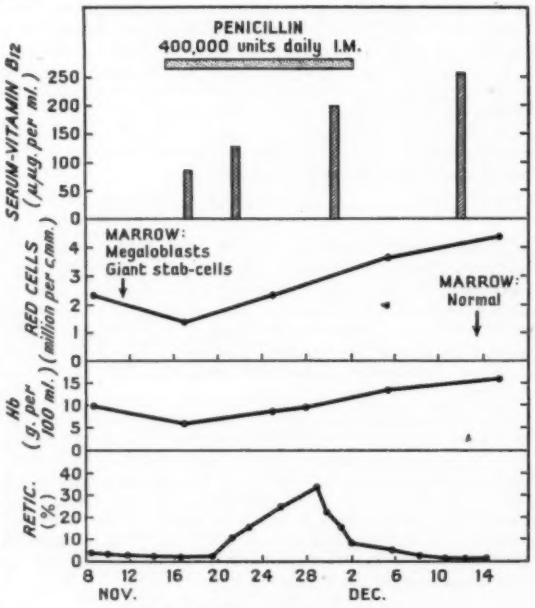

Fig. 1—Case 1: response to penicillin.

Drug therapy.—Our usual method of treatment was first to give the patients penicillin 400,000 units daily for 6–10 days; if there was no response, intramuscular vitamin B_{12} 80 μg. was given. Finally, if this failed to produce a response, folic acid was given by mouth. We think it important to follow this routine in this order, because all cases will respond to folic acid, but not all of them to intramuscular or oral vitamin B_{12}, or to penicillin.

SUMMARY OF SEVEN REPRESENTATIVE CASES

		Before treatment								After intramuscular penicillin							
Case no.	Sex	Hb (g. per 100 ml.)	Red cells (million per c.mm.)	P.C.V. (%)	Bilirubin (mg. per 100 ml.)	White cells (per c.mm.)	Serum-B_{12} (μμg. per ml.)	Sickling	Marrow	Hb (g. per 100 ml.)	Red cells (million per c.mm.)	P.C.V. (%)	Bilirubin (mg. per 100 ml.)	White cells (per c.mm.)	Serum-B_{12} (μμg. per ml.)	Stool-B_{12} (^{58}Co %)	Max. retic. (%)	Marrow
1	M	5·3	1·35	14·0	3·0	2350	100	Sickle-cell trait	Megal. G.S.C.	15·0	4·12	40·0	0·8	3·600	276	42	32·0	Normal
2	F lactating	5·2	0·80	9·0	1·5	8000	80	None	,,	11·8	4·02	40·0	0·4	3·150	98	52	48·0	,,
3	F	6·8	1·61	..	1·5	3060	20	None	,,	8·8	2·52	..	..	..	98	54	11·0	,,
4	F pregnant	3·0	1·16	8·0	1·5	3120	353	Sickle-cell trait	,,	2·2	1·00	..	2·0	..	1000	44	6·0	Megaloblasts and giant stab-cells
5	F pregnant	4·8	1·19	11·0	3·0	3300	1300	None	,,	3·8	0·90	..	..	..	1200	51	0·8	—
6	M	4·6	1·07	10·0	3·0	2350	1150	None	,,	2·4	0·60	..	..	..	1100	54	0·1	Megaloblasts and giant stab-cells
7	F	5·0	1·20	..	0·2	4400	550	None	,,	5·0	1·15	..	..	..	950	56	9·0	,,

Megal. = megaloblasts. G.S.C. = giant stab-cells. Max. retic. = maximum reticulocytosis.

Representative Case-histories

Case 1 (fig. 1 and table).—Typical megaloblastic anæmia in a male kept under observation for a week, during which there was no reticulocyte response and the red-cell count decreased from 2,200,000 to 1,350,000 per c.mm. and the hæmoglobin from 10·0 g. to 5·3 g. per 100 ml. From this point intramuscular penicillin o 400,000 units was given daily for 9 days. There was a complete blood response with a reversion of the marrow to normal. The serum-B_{12} level rose from a pretreatment level of 100 μμg. per ml. to 300 μμg.

42% of the administered dose of radioactive vitamin B_{12} was excreted.

Case 2 (fig. 2 and table).—Megaloblastic anæmia in a pregnant woman giving full response to intramuscular penicillin; serum-B_{12} level 80 μμg. per ml. before treatment and 98 μμg. 96 hours after the first dose of penicillin. No doubt, if the blood had been taken more than 96 hours after the first dose of penicillin a greater rise in the serum-B_{12} would have been found.

52% of the administered dose of radioactive vitamin B_{12} was excreted.

Case 3 (fig. 3 and table).—Typical megaloblastic anæmia in a non-pregnant girl of 18, with histamine-fast achlorhydria. There were definite signs of combined lesions of the posterior columns and pyramidal tracts characteristic of subacute combined degeneration of the cord; the gait was spastic, and the knee-jerks were exaggerated; both plantar responses were extensor; complete absence of vibration sense in both legs, although it was present in the arms. Pupils, cranial nerves, visual field, and abdominal reflexes normal. Tongue raw and smooth. Gastroscopy showed a normal mucosa with no gastric atrophy (Dr. G. C. Dockeray). Serum-B_{12} level 20 μμg. per ml. before treatment, rising to 98 μμg. after administration of penicillin but falling again to 40 μμg. and rising once more to 132 μμg. after administration of vitamin B_{12} 80 μg. by mouth. There was a submaximal increase in the reticulocytes, the red-cell count, and the hæmoglobin after administration of penicillin, followed by a decrease. After administration of vitamin B_{12} 80 μg. by mouth the reticulocytes increased to the expected maximum, and the red cells and hæmoglobin to 4,020,000 per c.mm. and 13 g. per 100 ml. respectively.

The responses to penicillin and to vitamin B_{12} 80 mg. by mouth indicate the presence of intrinsic factor, although perhaps in diminished amounts. The megaloblastic anæmia, the histamine-fast achlorhydria, the definite but early signs of nervous involvement, and the high excretion of radioactive vitamin B_{12} (78% of the administered dose) all suggest a pernicious anæmia in its very early stages. The absence of gastric atrophy as shown by gastroscopy could also be explained on the assumption that the disease was in its early stages. Perhaps a gastric biopsy would have shown some atrophy. The patient is being followed, and the biopsy will be done in 6 months. The amount of vitamin B_{12} made available after administration of penicillin was probably insufficient,

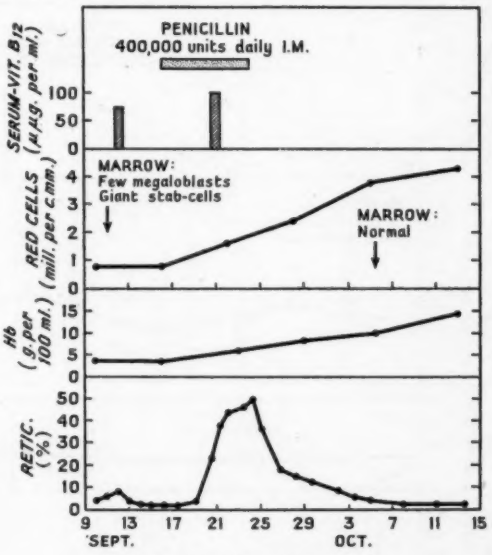

Fig. 2—Case 2: response to penicillin.

with the diminished amount of intrinsic factor, to maintain blood regeneration, whereas the greater quantity of vitamin B_{12} available after administration of vitamin B_{12} 80 μg. led to a higher rise in the serum-B_{12} level and a more sustained blood regeneration.

Case 4 (fig. 4 and table).—Characteristic megaloblastic anæmia in a pregnant woman with a long history of watery diarrhœa but no pathogens in the stools and normal fat-content. Gave a submaximal reticulocyte response to intramuscular penicillin, but no blood regeneration. Maximal and typical reticulocytosis and blood regeneration followed the administration of folic acid. Serum-B_{12} level 350 μμg. per ml. before treatment, rising to 1000 μμg. 2 weeks after the start of penicillin therapy.

44% of the administered dose of radioactive vitamin B_{12} was excreted in the fæces.

Case 5 (fig. 5 and table).—Typical megaloblastic anæmia in a pregnant woman with a history of 15 days' watery diarrhœa with no pathogens in stools and normal fats. There was no response to either penicillin or vitamin B_{12} 80 μg. by intramuscular injection, in fact the blood picture seriously deteriorated during treatment with penicillin and intramuscular vitamin B_{12}. Complete blood response to oral folic acid. Serum-B_{12} level 1300 μμg. per ml. before treatment,

SUMMARY OF SEVEN REPRESENTATIVE CASES

After vitamin B_{12} 80 μg.					After folic acid						
Hb (g. per 100 ml.)	Red cells (million per c.mm.)	Serum-B_{12} (μμg. per ml.)	Max. retic. (%)	Marrow	Hb (g. per 100 ml.)	Red cells (million per c.mm.)	Bilirubin (mg. per 100 ml.)	White cells (per c.mm.)	Serum-B_{12} (μμg. per ml.)	Max. retic. (%)	Marrow
..	..	..	..	..	..	..	..	..	..	..	..
..	..	..	..	..	..	..	..	..	..	..	..
13·0	4·00	132	18·0	Normal	..	..	..	..	..	..	..
Vitamin B_{12} not given		..	..	..	6·8	3·04	1·0	3·450	..	47	Normal
2·0	0·65	1100	0·7	..	9·8	3·28	0·6	5·250	1300	50	,,
2·5	0·70	1200	0·1	..	9·5	3·67	..	..	1100	46	,,
Vitamin B_{12} not given		..	..	..	13·0	4·50	..	6·800	..	38	,,

Max. retic. = maximum reticulocytosis.

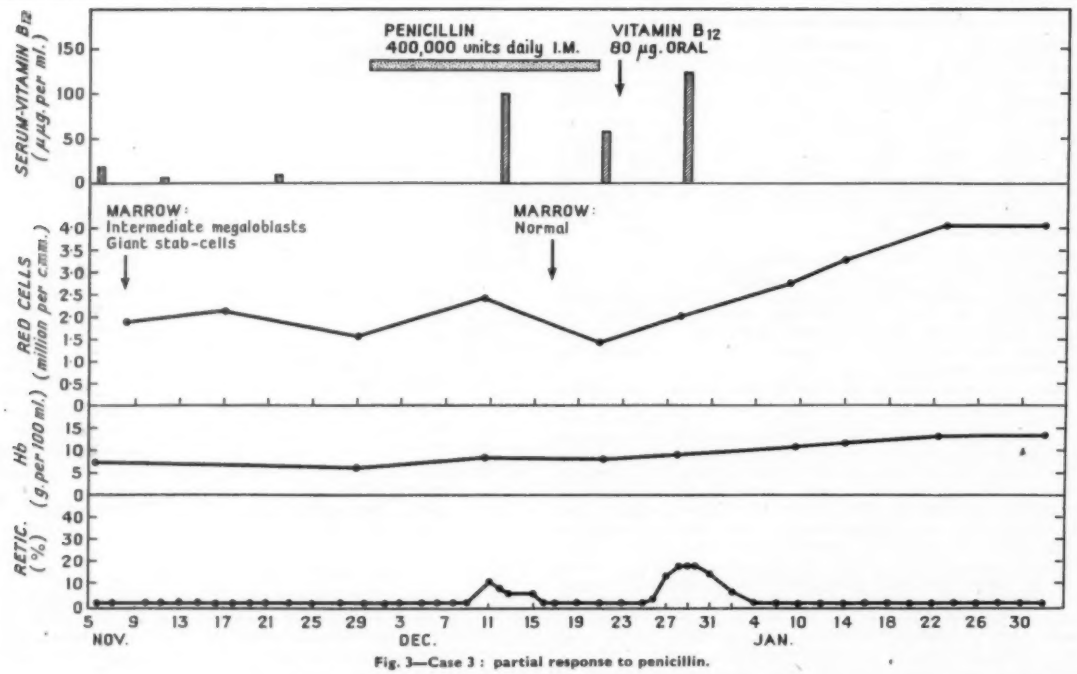

Fig. 3—Case 3 : partial response to penicillin.

showing no increase after administration of penicillin or of vitamin B_{12}.

51% of the administered dose of radioactive vitamin B_{12} was excreted in the fæces.

Case 6 (fig. 6 and table).—Megaloblastic anæmia in a male that did not respond to either penicillin or intramuscular vitamin B_{12} 80 µg. and red-cell count and hæmoglobin dropped during treatment with these substances. Maximal reticulocytosis and blood response to folic acid. Serum-B_{12} 1150 µµg per ml. before treatment, not influenced by either penicillin or vitamin B_{12}.

54% of the administered dose of radioactive vitamin B_{12} was excreted in the fæces.

Case 7 (fig. 7 and table).—Megaloblastic anæmia in a non-pregnant woman with a long-standing history of watery diarrhœa without pathogens in the stools and with normal fats. Emaciated patient. No response to penicillin, but maximum reticulocytosis and blood regeneration followed administration of folic acid. Serum-B_{12} 500 µµg. per ml., rising to 950 µµg. 10 days after commencement of penicillin treatment.

56% of the administered dose of radioactive vitamin B_{12} was excreted in the fæces.

Discussion

Cases Responding to Penicillin

Figs. 1–3 show that the patients with megaloblastic anæmia who responded to penicillin all had low pre-treatment serum-B_{12} levels (20–100 µµg. per ml.). After the administration of penicillin the reticulocytes increased to the maximum for the related blood-count in 6–12 days, and red cells and hæmoglobin doubled in 14–21 days from the start of treatment (Foy and Kondi 1953a and b). The marrow returned to the normoblastic picture, and the patients usually left hospital with normal red-cell counts and hæmoglobin. From 10 to 21 days after the start of treatment the serum-B_{12} level rose to twice or thrice its height but did not reach very high levels during the time we had our cases under observation. Perhaps this was because the tissues were depleted of vitamin B_{12} or because we did not allow enough time to elapse from the start of treatment to our estimation of the serum-B_{12}.

The excretion of radioactive vitamin B_{12} after the administration of penicillin in these cases responding to penicillin was of the normal pattern, only 30–55% being excreted in the stools. Meyer et al. (1953) have shown that there is great variability in the excretion of radioactive vitamin B_{12} in the fæces of the same person tested at different times, both in pernicious anæmia and

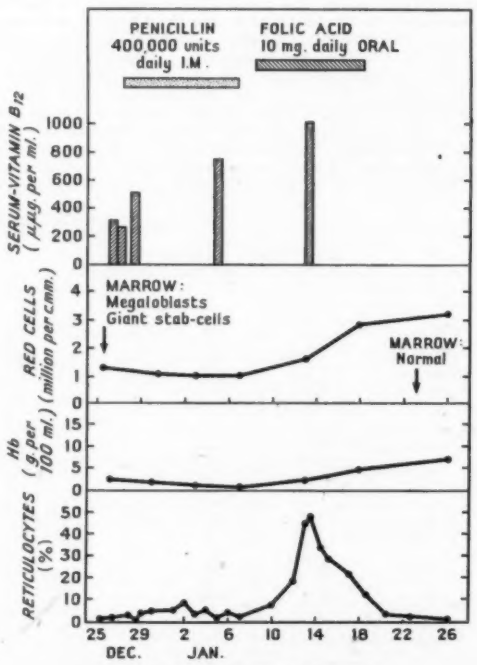

Fig. 4—Case 4 : response to folic acid.

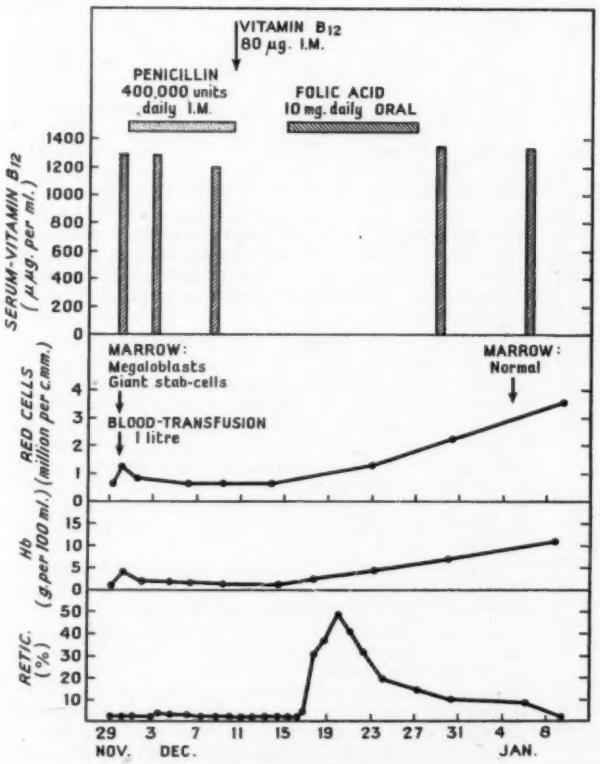

Fig. 5—Case 5 : response to folic acid.

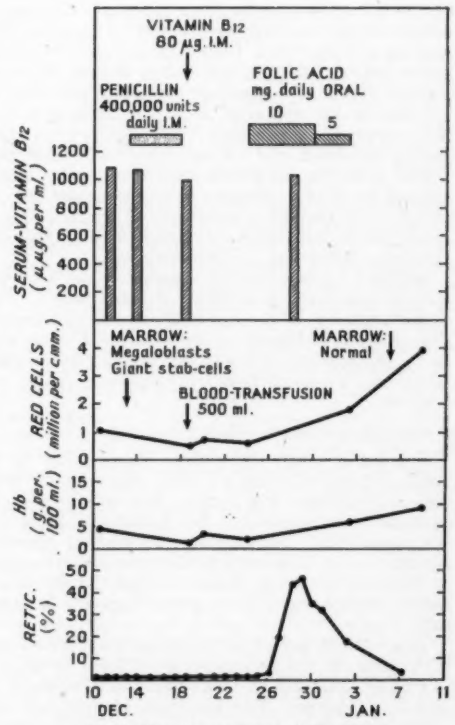

Fig. 6—Case 6 : response to folic acid.

in normal patients, and they regard the excretion pattern as too variable to permit of any critical comparisons. However, Halsted et al. (1954), Heinle et al. (1952), and Callender et al. (1954) hold that a high fæcal excretion-rate of radioactive vitamin B_{12} indicates diminished absorption due to either absence of or reduction in the amount of intrinsic factor. If this interpretation is correct, the excretion pattern of radioactive vitamin B_{12} seems to indicate that in the non-pernicious megaloblastic anæmias of Africans the absorption of vitamin B_{12} is normal, showing the presence of intrinsic factor. This view is substantiated by the clinical picture and the response to penicillin or to 80 µg. of oral vitamin B_{12}.

The excretion of radioactive vitamin B_{12} was estimated in all our cases after the administration of penicillin or of folic acid. Possibly this affected the excretion levels by increasing absorption from the lumen of the gut, a view that would fit in with the rise in the serum-B_{12} level after administration of these substances. It has been found that in chicks there are changes in the intestinal mucosa after administration of penicillin, and similar changes may occur in these anæmias, particularly when one remembers the effect that folic acid has on the diarrhœa in the cases that respond to folic acid.

From these results it is clear that antibiotics increase the serum-B_{12} levels; but whether this increase is due to improved absorption or to reduction of the organisms competing for vitamin B_{12} or to metabolic changes in the host is not yet known. None of the present patients had sore tongue, nervous symptoms, gastric atrophy, or achlorhydria.

Cases Responding to Folic Acid

The cases responding to folic acid (figs. 4–7) were in sharp contrast to those which responded to penicillin. They gave no response to either penicillin or to intramuscular vitamin B_{12}. After the administration of oral

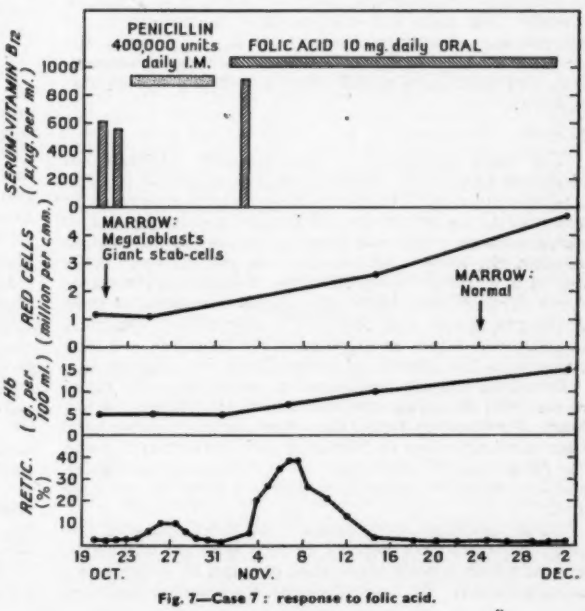

Fig. 7—Case 7 : response to folic acid.

folic acid there was, however, an increase in the reticulocytes to the expected maximum in 5–8 days, a doubling of the red cells and hæmoglobin in 14–21 days, and a return of the marrow to normal. The serum-B_{12} level was always high (300–1300 μμg. per ml.). Patients with levels below 700 μμg. showed a rise in the level and a slight reticulocytosis after penicillin, but there was no increase in the red cells or in the hæmoglobin. Those with serum-B_{12} levels above 700 μμg. per ml. showed no rise in the level and no reticulocytosis after penicillin.

The excretion of radioactive vitamin B_{12} was of the normal pattern, indicating the presence of intrinsic factor and normal absorption of vitamin B_{12}. This group had no nervous involvement, sore tongue, or gastric atrophy; some had hypochlorhydria.

A few of our patients responding to folic acid had watery diarrhœa, sometimes of many weeks' duration; no pathogens were present in the fæces, and the diarrhœa nearly always cleared up on treatment with folic acid. In those cases where it did not do so, kaolin was always effective; we never found it necessary to give sulphonamides.

Pernicious Anæmia

The patient with pernicious anæmia (fig. 3) had the usual pernicious-anæmia blood picture with histamine-fast achlorhydria, sore tongue, and definite signs of early nervous involvement. The serum-B_{12} level was low (20 μμg. per ml.). Gastroscopy showed no signs of gastric atrophy; but it is known that gastroscopy alone is not an infallible means of diagnosis, and it may well be that gastric biopsy would have revealed gastric atrophy in its early stages.

This patient gave a submaximal response to penicillin, with a rise in the serum-B_{12} level from 20 μμg. per ml. to 98 μμg. followed by a submaximal increase in red cells and hæmoglobin. The first test of excretion of radioactive vitamin B_{12} gave a value of 54%, and the second one, after treatment with penicillin and vitamin B_{12}, a value of 78%. We think that this was an early case of pernicious anæmia with some intrinsic factor, which gradually decreased in hospital.

We have previously described a case similar to this (Foy and Kondi 1953a and b) with histamine-fast achlorhydria but no gastric atrophy and giving a submaximal response to penicillin; this patient later developed typical gastric atrophy and then did not respond to penicillin but responded to intramuscular vitamin B_{12}. Evidently the presence of intrinsic factor is not an all-or-none phenomenon, and such cases usually pass into typical pernicious anæmia.

Diet

The high incidence of megaloblastic anæmias in countries like India, Africa, and Macedonia is of considerable interest. The diet in these countries is generally admitted to be low in animal protein and rich in bulky carbohydrates. Whether this type of diet is deficient in vitamin B_{12} and/or folic acid is not yet known. Since diet is a factor in the production of such syndromes as sprue (Frazer 1949, 1953) and affects the bacterial flora of the gut, it may well be that the type of diet consumed in countries where megaloblastic anæmias are common encourages the growth of competitors for vitamin B_{12}.

Intestinal bacteria are known to produce a wide range of essential vitamins, many of which are utilised by the host. Perhaps the diet of the countries in which we have been working is low in folic acid and/or vitamin B_{12} and the inhabitants depend more on the vitamin B_{12} synthesised by their intestinal flora than do those on a better diet.

These anæmias are seasonal: at some times of the year the types that respond to folic acid are numerous, and at other periods those that respond to vitamin B_{12} are commoner. We have observed this seasonal incidence in Macedonia, Africa, and the Fiji Islands. It seems likely that it is associated with dietary differences.

The low serum-B_{12} levels in the anæmias that respond to penicillin may be due to deficiency of vitamin B_{12} in the diet, or to the presence of competitors for vitamin B_{12} in the gut, or to failure in absorption of vitamin B_{12}.

In the non-megaloblastic microcytic iron-responding anæmias, the serum-B_{12} level is always either normal or high. These patients presumably eat the same type of diet, and the implication seems to be that this does not lack vitamin B_{12}. Further, the stools of our patients with megaloblastic anæmia contain 50–80 μg. of vitamin B_{12}; but we do not know whether this is of dietary origin or synthesised by intestinal bacteria, and locked up in them, and therefore not available to the host.

Intestinal Flora

It is generally assumed that, since the vitamin B_{12} is synthesised in a part of the gut where there is no intrinsic factor it is not available for hæmopoiesis. The responses obtained in pernicious anæmia from small doses of vitamin B_{12} either given by mouth or sprayed into the nose suggest that besides intrinsic factor and mass action other factors may be concerned in the absorption of vitamin B_{12} (Harte and Chow 1953, Monto et al. 1954, Chalmers and Hall 1954, Watson 1950, Barnett 1932, Welch and Heinle 1951, Israëls and Shubert 1954).

Whether defects in absorption are responsible for the low serum-B_{12} levels or not is more difficult to decide. The fact that our patients had a normal pattern of excretion of radioactive vitamin B_{12} and no achlorhydria, and responded to penicillin or to vitamin B_{12} 80 μg. by mouth suggests that intrinsic factor was present and absorption normal. We are then left with the possibility that the gut contains bacteria competing with the host for the dietary vitamin B_{12}, and that penicillin acts by destroying these and/or releasing by lysis their contained vitamin B_{12}, which would explain the rapid response that follows administration of penicillin.

It is well known that the megaloblastic anæmia due to diphyllobothrium infection can be cured either by removing the worm or by giving vitamin B_{12}; the worm contains large quantities of vitamin B_{12} of which it must have deprived its host. Many groups of bacteria are avid for vitamin B_{12}; such bacteria are present in the upper gut of pernicious-anæmia patients, and evidence is accumulating that they occur in other conditions also (Davidson 1928, Watson 1950).

The megaloblastic anæmias that develop in patients and animals with self-filling intestinal loops can be prevented and cured with antibiotics, which probably act on the flora of the gut (Naish and Capper 1953, Cameron 1949, Hausmann et al. 1954, Pearson 1954). The evidence that antibiotics stimulate growth in many different groups of animals is now overwhelming (Stokstad 1954, Rhodes et al. 1954), and it is generally accepted that they do so by affecting the bacterial flora of the gut.

Serum-B_{12} Levels

In the present cases the rises in the serum-B_{12} level after administration of penicillin were from twofold to sixfold, but the peak was not reached until 2–4 weeks after the commencement of treatment. The reticulocyte peak, however, was attained in 3–6 days, and red-cell and hæmoglobin values doubled themselves in 2–3 weeks—in fact in about the same time as is required to reach the peak after administration of vitamin B_{12} 80 μg. (oral or intramuscular). Ross et al. (1954) report that serum-B_{12} levels in their cases reached the peak in 3–6 hours after the administration of 500–3000 μg. of oral vitamin B_{12}. These workers think that 5 μg. of vitamin B_{12} absorbed from the intestinal tract can produce a detectable rise in the serum-B_{12} level, and that in none of their cases was there a hæmatological response without a rise in the serum-B_{12} level. They further suggest that

the absorption of 1 μg. of vitamin B_{12} from the gut would be unlikely to produce a detectable rise in the serum-B_{12}. Probably, therefore, the amount of vitamin B_{12} made available by the administration of penicillin would be greater than 1 μg., and this might continue for a long time. The first amounts made available would be immediately used in hæmopoiesis, and only when hæmopoiesis was satisfied would there be a gradual saturation of the serum, with a consequent rise in the serum-B_{12} level at the end of 2–3 weeks or more.

Summary

Classified according to their response to treatment, there are at least two types of non-pernicious megaloblastic anæmia in Africans.

One type responds completely to penicillin (oral or intramuscular) or to vitamin B_{12} 80 μg. by mouth. In these the level of vitamin B_{12} in the serum, as estimated with *Euglena gracilis*, is very low before treatment; but in 2–4 weeks after the start of treatment it is doubled or trebled. Free acid is present in the gastric juice after the administration of histamine, and the excretion of radioactive vitamin B_{12} after treatment with penicillin is 35–55% of the administered dose. The most probable explanation of the response to penicillin in this type of anæmia is that the antibiotic destroys micro-organisms in the gut which compete with the body for vitamin B_{12}.

The other type of megaloblastic anæmia does not respond to either penicillin or intramuscular vitamin B_{12} 80 μg. but does respond to folic acid by mouth. Before treatment the serum-B_{12} levels range from normal to very high. Free acid is present in the gastric juice, and after administration of folic acid the excretion of radioactive vitamin B_{12} in the fæces is of the normal pattern.

The absence of gastric atrophy on gastroscopy, the presence of free acid in the gastric juice, and the normal excretion of radioactive vitamin B_{12} all seem to indicate the presence of intrinsic factor and normal absorption, at least after treatment.

The incidence of these anæmias varies with the season, probably because of variations in diet, which may favour (or otherwise) the growth, in the intestine, of bacterial competitors for hæmopoietic substances.

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HYPOTHERMIA IN THE TREATMENT OF A CASE OF POSTPARTUM HÆMORRHAGE

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A WOMAN, aged 39, a 5-gravida with a normal obstetric history, was spontaneously delivered in her home of a healthy child at 5.15 P.M. on Jan. 11, 1955, after a normal pregnancy and labour. Third-stage hæmorrhage was excessive, and her doctor expressed the placenta at 5.25 P.M. Because of persistent uterine bleeding the Southern General Hospital obstetric emergency team was summoned at 7.10 P.M. When they arrived at 7.30 P.M., the patient was profoundly collapsed, her systolic blood-pressure being 40 mm. Hg.

First Resuscitation

Response to resuscitative measures was slow, and moderate bleeding continued. By 11.10 P.M., however, the blood-pressure appeared to be stabilised at 110/80 mm. Hg, and the patient was transferred to the Southern General Hospital, blood-transfusion being continued during the journey of four miles. When she was admitted to the labour ward at 11.30 P.M. her condition had not deteriorated, and the blood-pressure was 110/80 mm. Hg.

Checking the Hæmorrhage

The uterus was explored at midnight. A few scraps of membrane only were found in the uterine cavity, but there were extensive bilateral cervical lacerations with arterial bleeding, and these were sutured. Bleeding had ceased at the end of this operation but began again from the uterine cavity ten minutes later. The blood-pressure fell to 90/70 mm. Hg and did not respond to continued rapid intravenous transfusion. By 2.45 A.M. on Jan. 12 the patient had become extremely restless. Effective sedation was achieved by intramuscular chlorpromazine 25 mg. and promethazine 25 mg. A similar injection was repeated at 5.45 A.M. and 6.15 A.M. In spite of conventional methods of treatment, moderate uterine bleeding continued, and the patient's condition deteriorated steadily.

At 3.15 A.M., under ether and oxygen anæsthesia, the uterus and vagina were packed. During this operation the systolic blood-pressure, which had been 95 mm. Hg, dropped to 45 mm. Noradrenaline, 4 mg. to the pint, added to the blood-transfusion met with an immediate response, the systolic blood-pressure thereafter being maintained at 110–120 mm. Hg by constant adjustment of the infusion-rate. In addition, it was necessary to increase the concentration of noradrenaline by stages to 32 mg. per pint of infusion, to restrict the input of fluid. Just over an hour after the uterus and vagina had been packed the packs had become saturated and frank bleeding per vaginam recommenced. Hysterectomy was considered but rejected because it was thought that the patient would not survive the operation. Despite this, the blood-pressure was maintained at about 110/80 mm. Hg with noradrenaline but became unrecordable at once if the infusion was stopped, even for a few seconds, as when blood-flasks were being changed. The pulse-rate was 125–140 per min., the peripheral circulation was poor, and signs of cerebral anoxia were becoming prominent.

By 8.45 A.M. the patient appeared to be moribund. Her blood-pressure, however, continued to respond to intravenous noradrenaline. It was clear that hysterectomy offered the only hope of recovery, all other methods of treatment having failed to control the uterine hæmorrhage. As she was unfit for operation under conventional anæsthesia, it was decided that hypothermia should be used.

Hypothermia

It would have been unsafe to move the patient; so refrigeration was begun in the labour room. The "lytic cocktail," a mixture of chlorpromazine 50 mg., promethazine 50 mg., and pethidine 100 mg., was injected intravenously in four equal divided doses at ten-minute intervals from 10.30 A.M. Ice-bags were applied to the patient's axillæ, groins, abdomen,

and chest after the second injection. At 10.45 A.M. 4 ml. of a 5% solution of thiopentone was injected intravenously together with suxamethonium chloride 25 mg. to permit orotracheal intubation with a no. 9 Magill cuffed endotracheal tube. Anæsthesia was maintained with a Boyle's machine, semi-closed, with a 50% mixture of nitrous oxide and oxygen at a flow-rate of 8 litres per min. At 11.45 A.M., with her rectal temperature 37°C, pulse-rate down from 140 to 120 per min., improved colour, and more adequate respiratory exchange, it was possible to transfer the patient to the anæsthetic room, which had been drastically cooled to receive her.

Hysterectomy

The patient was taken into the operating-theatre at 12.15 P.M., when her rectal temperature was 35°C. There had been further improvement in her colour, and her pulse-rate had fallen to 88 per min. Muscular relaxation was obtained with intravenous *d*-tubocurarine chloride 20 mg. Anæsthesia was maintained with a Waters apparatus using a 50% mixture of nitrous oxide and oxygen, with carbon-dioxide absorption.

Laparotomy revealed a postpartum uterus of normal size, firmly retracted on the intra-uterine pack. There was no evidence of uterine rupture, and the uterine appendages were healthy. Subtotal hysterectomy was performed, the fallopian tubes and ovaries being conserved, and subsequent inspection of the vaginal vault showed the cervical stump and vagina to be dry. A light vaginal pack was inserted. On completion of the operation at 1.5 P.M. the rectal temperature was 34°C (93°F), the systolic blood-pressure had been maintained between 105 and 120 mm. Hg throughout, and the pulse-rate remained at 88 per min. After operation neostigmine 1 mg., nikethamide 2 ml., and atropine sulphate 0·325 mg. were given intravenously to eliminate residual muscular relaxation.

Rewarming

It was decided to allow spontaneous rewarming. The patient was covered by one sheet only, and instructions were given to add blankets as necessary, the danger of allowing shivering being emphasised. Oxygen was administered continuously, at a rate of 6 litres per min., through a nasopharyngeal catheter. The blood-pressure was read as often as was necessary for adjustment of the noradrenaline infusion, and the rectal temperature and pulse-rate were recorded at fifteen-minute intervals.

Return towards normal temperature was not accompanied by stabilisation of the blood-pressure. By the late evening of Jan. 12 the rectal temperature was 39·8°C (104°F) and the pulse-rate had risen, being above 200 per min. at midnight. The patient's condition was again critical. Recooling was started by intravenous injections of the "lytic cocktail" and the application of ice-bags, until, by 3 A.M., the rectal temperature had fallen to 37·6°C. Between 3 A.M. and 5 A.M. the pulse-rate dropped from over 200 to 140 per min. and the rectal temperature fell to 35°C. Cooling was continued until, at 8 A.M., with the rectal temperature at 33°C, the picture appeared more hopeful.

In the light of this experience, it was decided to allow rewarming to proceed only to 35°C, the degree of recovery of vasomotor function then determining whether further rewarming should be allowed, or whether the hypothermic state should be maintained. By noon on Jan. 13 the temperature of 35°C was reached, and in the early afternoon the blood-pressure was found to be recordable (85/50 mm. Hg) for the first time without the aid of noradrenaline, which was discontinued, hourly intramuscular injections of 15 mg. of methylamphetamine being substituted. Between noon and 4 P.M. the patient had five brief generalised convulsions. After the first convulsion, the administration of oxygen by nasopharyngeal catheter was discontinued, and she was placed in an oxygen tent. At 5 P.M. her blood-pressure was 90/50 mm. Hg, rectal temperature still 35°C, and pulse-rate 120 per min. Intramuscular injections of methylamphetamine 15 mg. and of nikethamide 1 ml. were now given alternately at half-hour intervals. By 10 P.M. the temperature had risen to 35·8°C, and the systolic blood-pressure remained between 110 and 120 mm. Hg.

On the morning of Jan. 14 the prognosis seemed to be improving, and, the systolic blood-pressure remaining at 105–110 mm. Hg, the methylamphetamine and nikethamide injections were stopped. As the day progressed, however, the rectal temperature rose, reaching 38·8°C at 5 P.M., when the clinical picture was very depressing. The patient was delirious, had become difficult to control, and had aural and visual hallucinations. Intramuscular morphine sulphate 8 mg. was given at 7 P.M. and at 9 P.M. without apparent effect, and morphine sulphate 16 mg. at 11 P.M. produced only transitory sedation. The patient spent a very restless and exhausting night, and at 9 A.M. on Jan. 15 her condition was desperate. It was decided to provide sedation and fluids by the rectal infusion of physiological saline solution, with 8 fluid drachms of paraldehyde to the pint. This proved effective, 2 pints being given, and was continued by the infusion of 2 pints of 5% dextrose in sixteen hours, only the first pint containing 8 fluid drachms of paraldehyde.

On the morning of Jan. 16, the patient having remained adequately sedated throughout the night, and her blood-pressure having been maintained, her pulse-rate was 124 and rectal temperature 37·4°C. She was now receiving a rectal infusion of 5% dextrose without paraldehyde but remained very much under the influence of paraldehyde. Her general condition remained satisfactory during the day. In the late evening she regained consciousness sufficiently to respond when spoken to, and all signs of cerebral irritation had disappeared.

The Outcome

Subsequent progress was steady and uneventful. A small quantity of milk could be expressed from the breasts by the fifth postnatal day. In view of the large volume of intravenous fluid administered in the forty-eight hours following her delivery, the absence of respiratory complications was remarkable. A burn on her left leg, about 20 cm. by 10 cm. in extent, caused by a hot-water bottle before her admission to hospital, was excised and grafted with multiple postage-stamp grafts on Feb. 2 under general anæsthesia. Her general condition by this time was excellent, and her subsequent stay in hospital was entirely due to the burn. She was discharged on March 4, the 66th postnatal day.

The patient was readmitted from Sept. 16 to 17 for assessment of her condition. The findings were:

General physical condition satisfactory. Blood-pressure 110/65 mm. Hg. Urine dilution and concentration tests normal. Hæmoglobin 13·8 g. per 100 ml. Blood-sugar (random sample) 135 mg. per 100 ml. Blood-urea 31 mg. per 100 ml. Serum-electrolytes: sodium 129 m.eq. per litre, potassium 4·24 m.eq. per litre, chlorides 97·5 m.eq. per litre (as NaCl). CO_2-combining power of plasma 76·2 vols. %. X-ray of chest negative. Electrocardiograph normal.

Discussion

The decision to use hypothermia in this case stemmed from our own experience of the technique and from published reports. Our results were in accordance with the claims of those who regard this type of potentiated anæsthesia as a means of allowing surgery on patients formerly considered unfit for operation (Smith and Fairer 1953, Dundee and Mesham 1954, Palomba and Marogna 1954, Remé 1954, Hopkin 1954).

In spite of the vigorous use of conventional methods to combat the effects of the persistent bleeding and shock, the condition usually regarded as irreversible shock was present when hysterectomy was decided on—the sole favourable feature being the continued response to infusion of noradrenaline. The choice of operating under potentiated anæsthesia or not at all had to be made. Refrigeration was carried out by the technique utilising intravenous injection of the "lytic cocktail" to facilitate the fall in body-temperature produced by surface cooling (Dundee et al. 1953, Dundee and Mesham 1954).

Two points require special mention in a case such as this:

(1) Every effort must be made to maintain the circulating blood volume at an adequate level before injecting intravenously the "lytic cocktail" containing chlorpromazine, because of the danger in producing peripheral vasodilatation when the circulating volume is deficient (Millar 1954, *Anæsthesia* 1955). If, however, a state of irreversible shock obtains, peripheral vasodilatation is beneficial (Evans 1954), provided the circulating volume remains adequate.

(2) Cooling measures must be vigorous, or the patient's temperature may rise. One of the advantages of hypothermia is the consequent decrease in the oxygen requirement of the tissues as cooling proceeds (Bobbio and Goffrini 1952, Dundee et al. 1953, Dundee and Mesham 1954, Juvenelle 1954, Bigelow et al. 1954). The "lytic cocktail," and in particular chlorpromazine, upsets thermoregulation (Courvoisier et al. 1953, Dundee et al. 1953, Churchill-Davidson 1954, Kopera

and Armitage 1954) and in effect converts the subject from being homeothermic to being poikilothermic, the body-temperature then varying with the environmental temperature (Shackman et al. 1954). An initial rise in temperature may be of little significance when preparing for elective surgery, even in a "poor risk" case, but the shocked patient cannot suffer with impunity any increased demand for oxygen, such as would accompany a rise in temperature.

After operation it was hoped that, as rewarming proceeded, so would vasomotor function recover; but this did not occur. Prolongation of hypothermia after the operation might have avoided much of the subsequent danger in this case (Remé 1954), or, by keeping the patient under the influence of chlorpromazine, the post-operative course might have been favourably influenced (Hopkin 1954). Eleven hours after hysterectomy the action of the heart was giving rise to great anxiety, and one of the major benefits expected of recooling was reduction of tachycardia, with an improvement in cardiac output. The concurrent administration of chlorpromazine and noradrenaline might have been expected to have an adverse effect on the heart-rate (Foster et al. 1954). However, it was found that although, as cooling proceeded, the heart-rate did fall, it was not until the rectal temperature had fallen to 33°C that any hope of the patient's survival could once more be entertained.

It is worth noting that, after the second period of hypothermia, this patient had no sleep until she was given paraldehyde. In retrospect it appears that heavier sedation at an earlier stage would have been advantageous. The wakefulness is thought to have been caused by, and in turn contributed to, the cerebral irritation which the patient displayed.

The omission of one method of resuscitation—viz., intra-arterial transfusion—will undoubtedly have been noted by the reader. The deterioration in the patient's condition up to the time of packing the uterus and vagina was due to a more or less steady blood-loss over nearly four hours. Blood-transfusion during this period was more than adequate to replace the loss, and the systolic blood-pressure had remained at or about 90 mm. Hg and thus did not demand this method of resuscitation. Unfortunately, packing of the uterus and vagina produced considerable additional shock, and the accompanying onset of acute hypotension presented the first indication for intra-arterial transfusion while in hospital. The change in the patient at this point was so alarming that the most readily available and effective means of restoring the blood-pressure had to be used. This was undoubtedly the addition of noradrenaline to the blood-transfusion, which produced an immediate response.

Intravenous therapy included 1·87 litres of blood and 0·57 litre of dextran before admission, followed by a further 8 litres of blood, 1·1 litres of physiological saline solution, and 2·8 litres of 5% dextrose. The fluid balance from Jan. 12 to Jan. 21 is shown in the accompanying table.

The blood-urea level reached its peak on the seventh postnatal day, when it was 55 mg. per 100 ml.; and on the eighth, ninth, and tenth postnatal days it was 44 mg., 37 mg., and 37 mg. per 100 ml. respectively.

The possibility that irreversible damage due to anoxia had taken place, particularly to the kidneys, pituitary gland, and suprarenal glands, was a constant source of anxiety.

INTAKE AND URINARY OUTPUT

(Excluding whole blood and dextran)

Date (Jan. 1955)	Intake (ml.)	Output (ml.)	Date (Jan. 1955)	Intake (ml.)	Output (ml.)
12	3978	57	17	1307	710
13	4035	739 + *	18	1023	710
14	852	3496	19	1421	852
15	2274	852	20	795	511
16	1279	852	21	540	596

* Incontinence of urine.

There can be little doubt that reduction in the oxygen requirement of the tissues brought about by hypothermia in the critical phases must have contributed substantially to the protection of these organs and to the survival of the patient.

Summary

The use of hypothermia in the treatment of a case of postpartum hæmorrhage with apparently irreversible shock is described and discussed.

Hypothermia is regarded as a supplement to and not a substitute for, orthodox resuscitative measures.

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RESUSCITATION FROM "IRREVERSIBLE" SHOCK BY INTRA-ARTERIAL TRANSFUSION

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MANY cases of intra-arterial transfusion have been reported. Exsanguination and shock from various causes were the indications for its use. These causes included hæmorrhage, toxæmic states due to peritonitis or to loss of body-fluids, and postoperative shock which could not be overcome by intravenous transfusion.

All reports bear witness to the superiority of the intra-arterial over the intravenous route: recovery was more rapid and better sustained, and resuscitation was successful when intravenous transfusion had either failed or held out no prospect of success. Recovery is described in cases of very severe shock, in some of which cardiac and respiratory arrest had supervened (Negovsky 1945, Bilsland 1951, Haxton 1952, 1953, Good 1953, Pryer 1953, Horton et al. 1953).

In contrast with this unanimity of clinical opinion, there is no generally accepted view on the mode of action of intra-arterial transfusion. Current thought on this problem and the reported superiority of intra-arterial transfusion have been questioned (Maloney et al. 1953). It would be unfortunate if ignorance of its mode of action were to lead to prejudice against a measure which can save life—a virtue which the following case-record may help to demonstrate.

Case-record

Mrs. A, aged 37, was admitted to King George Hospital, Ilford, on May 18, 1954. She had aborted a 12–16 weeks' fœtus 5 days before admission and had continued to lose bright-red blood. She had had two previous pregnancies. The second, which had been of twins, had involved the manual removal of a morbidly adherent placenta and a blood-transfusion later for secondary postpartum hæmorrhage. Her previous health had been good.

On admission she was pale and cold, with a muddy complexion; blood-pressure 95/70 mm. Hg, and pulse-rate 128.

In the ward she was given morphine gr. $^1/_4$ and intravenous 'Dextraven' and blood, two pints of each. At 5 P.M. her blood-pressure was 110/70 mm. Hg, pulse-rate 120, and skin warm but still sallow. She was given atropine gr. $^1/_{100}$ and at 5.30 P.M. was taken to theatre.

Anæsthetic

Anæsthesia was induced with thiopentone 0·3 g., nitrous oxide/oxygen, and a minimal amount of trichloroethylene. When uterine hæmorrhage could not quickly be controlled, light ether was substituted for trichloroethylene, in view of the probable need for noradrenaline. Control took about an hour from the time of induction, but anæsthesia had to be continued thereafter to control the restlessness of profound shock. Gas and oxygen alone were then used (5 and 3 litres per min. respectively), except when trichloroethylene was added for short intervals before the repeated bronchial suction which pulmonary œdema made necessary.

Operation

The patient was examined under anæsthesia by Miss Valerie Thompson, gynæcological registrar. In the vagina and uterus was 30 oz. of blood-clot. The wall of the uterus felt thin and flabby. The uterus gave forth a fœtid smell. The placenta was morbidly adherent in two places and was removed manually. Profuse bleeding followed. The uterus did not react to intravenous ergometrine, bimanual compression, repeated massage, or (finally) hot intra-uterine douches. Because of rapid deterioration in the patient's condition the uterus was packed and bimanually compressed on the pack; this slowed and then stopped the bleeding.

Resuscitation

The patient had arrived in the operating-theatre with an intravenous dextrose-saline drip in the left arm. This drip had been set up in the ward and was continued throughout the resuscitation except for one short interval.

Within 15 minutes of induction of anæsthesia blood was substituted for the dextrose-saline solution because of rapid blood-loss, which led to shock. Rapid transfusion of dextrose-saline solution did not avert or reverse the steady drop in blood-pressure. Neither did two pints of blood streamed in under pressure, the second containing noradrenaline 2 mg., although most of the blood just lost was now considered to have been replaced. A further rapid transfusion was begun of a third pint of blood containing noradrenaline 8 mg. The systolic blood-pressure was thereby raised from unrecordable to 110 mm. Hg, but the improvement was transient, and the pressure again became unrecordable. The carotid pulse alone could be felt—rate 130 and soft. The skin was cold and bloodless—finger pressure produced no blanching—but there appeared to be no resistance to the intravenous transfusion; blood could be streamed in without pressure from a pump. The drip was stopped temporarily.

The prognosis was exceedingly grave. Intravenous restoration of the blood volume had failed even to arrest the decline in the blood-pressure, let alone reverse it. The peripheral vascular reactivity and resistance appeared to have failed. In the light of these facts an intra-arterial transfusion was considered urgent, and surgical assistance was obtained to cut down on the right radial artery. Unfortunately the cannula was inserted into a vein instead of an artery, and this was not discovered until $4^1/_2$ hours later.

A further pint of blood was transfused rapidly through this vessel under the impression that it was the radial artery. The result was "disappointing," there being no change in the carotid pulse or in the blood-pressure. By this time the uterine bleeding had stopped.

The legs and thighs were bandaged towards the heart, and the head-down tilt of the table was increased. The intravenous drip in the left arm was started again, dextrose-saline solution following the remainder of the third pint of blood. The drip-rate was kept slow.

About half an hour after the patient's limbs had been bandaged her condition suddenly deteriorated further. Her face became pale blue; her carotid pulse became only just palpable; and her pupils were widely dilated and did not react to the laryngoscope light.

Oxygen and carbon dioxide were given. There was no improvement. The carotid pulse began to become irregular and then not palpable with certainty.

Nikethamide 8 ml. was injected via the drip tubing as fast as possible. This produced a convulsion (facial twitching and head retraction), hyperpnœa, and immediate improvement in the carotid pulse, which reappeared and became stronger. The cyanosis all but disappeared. The blood-pressure remained unrecordable, but a more peripheral pulse could be felt. The convulsion passed off after a minute or two.

At this moment the patient began to come out of anæsthesia and was very restless. To sedate her without further depressing her cardiovascular system gas-and-oxygen anæsthesia was re-established; and 50% sucrose 60 ml. was injected via the drip tubing. This was followed by deviation of the previously central eyeballs to the right and diminution of the pupils, which now reacted to a torch (but not to the laryngoscope light). To reduce any arterial spasm in the right arm caused by the "intra-arterial" transfusion the brachial plexus was blocked with lignocaine 20 ml. with adrenaline.

8.30 P.M.—Blood-pressure 80/60 by oscillometry, but this could not be confirmed by auscultation. The carotid pulse felt no stronger than immediately after the injection of nikethamide, and the skin remained pale, cold, and dry. It was decided that the patient's condition might be improved by the addition of ether to the anæsthetic; this necessitated giving atropine again because so long had elapsed since premedication. Ether was not pressed, because of a sudden deterioration after atropine gr. $^1/_{100}$ intravenously had been given; the pulse-rate rose sharply from 120 to 150, and the carotid pulse grew weaker. Oscillometry appeared to show a blood-pressure of 60/50.

Although the pulse-rate was successfully reduced to 120 by intravenous neostigmine (2 mg. in 0·5 mg. doses), the blood-pressure did not rise.

9.45 P.M.—Crepitations in the lungs could be heard from the head of the table: auscultation over the dependent parts of the lungs confirmed their presence. Intravenous strophanthin gr. $^1/_{125}$ was given to sustain the force of contraction of the myocardium. Poor coronary perfusion due to hypotension must have made the myocardium grossly hypoxic after this length of time. There was no observable effect from this injection during the next hour.

10 P.M.—Blind nasal intubation of the trachea was performed to facilitate bronchial suction. The pale-pink frothy fluid of pulmonary œdema was obtained. Suction was repeated as necessary.

11 P.M.—The pulmonary œdema was increasing rapidly, and it was obvious that the patient could not recover without active assistance, if she could be resuscitated at all. It was decided to "repeat" the intra-arterial transfusion. Surgical assistance was again obtained. The cannula, which had been left in situ, was then found not to be in the radial artery.

During the next half-hour while preparations were being made, bronchial suction had to be applied more frequently.

Intra-arterial Transfusion

The right radial artery was infiltrated with 2% procaine, which was also injected via the cannula before and after transfusion. The cannula was inserted retrogradely into the artery, which was afterwards severed between ligatures.

11.30 P.M.—Dextraven 200 ml., followed immediately by 1 pint of blood, was transfused rapidly under pressure. About seven minutes was needed for this, including time to change the bottles. Within about three minutes from the end of the transfusion the systolic blood-pressure, which had been unrecordable just before transfusion, rose to an unequivocal 85 mm. Hg by auscultation.

During the next half-hour colour and warmth began to return to the skin. Sweating began. Crepitations disappeared from the lungs, leaving high-pitched rhonchi and basal bronchial breath sounds. The bronchospasm was moderate and easily relieved by intravenous aminophyllin. The pulse-rate remained steady at 120, and the systolic blood-pressure was 80–90 mm. Hg. Respirations became rapid and deeper, and pethidine was given to moderate them and for its general effect.

Between midnight and 12.30 A.M. the operating-table was gradually levelled. No ill effects were seen to follow. The anæsthetic was discontinued and the endotracheal tube removed. The patient regained consciousness a minute later and vomited copious dark-brown "coffee-grounds," suggesting altered blood. She was immediately able to respond to requests, to open her mouth and shortly afterwards to answer simple questions rationally and coherently. Her improvement was maintained during another hour's observation in the theatre after removal of the bandages from her legs. She was therefore transferred to the ward in her bed. With the foot of the bed raised, her blood-pressure was 90/65. Her lung bases were dry; the intravenous drip was maintained.

Postoperative Course

She vomited "coffee-grounds" several times during the night. Her blood-pressure rose slowly to her normal 110/70, and her general condition remained good. At 11.30 A.M. the pack was removed from the uterus under light general anæsthesia. The uterus had contracted down well. The output of urine was normal in quantity and quality the same day and remained so. There was no evidence of damage to the central nervous system.

No peripheral damage from ischæmia followed ligation of the radial artery. A small area of analgesia over the metacarpophalangeal joint of the right thumb disappeared after several months. Uterine sepsis, probably present before operation, and sepsis in the forearm proximal to the cutting-down incision, were treated effectively with antibiotics.

A course of cortisone was started immediately to prevent Simmonds's disease. Careful search failed to reveal any evidence of endocrine disturbance. Normal menstruation returned, body-weight increased, and the output of 17-ketosteroids was normal. The patient returned to her normal life as a housewife. She has continued in good health and shows no signs of general or local harm from her experience.

Before operation the patient appeared to have been completely and easily resuscitated from her state of shock on admission. No collapse of blood-pressure followed induction of anæsthesia.

The radial artery was difficult to distinguish from its associated veins: procaine infiltration had softened it, and a tourniquet had stopped its pulsation. In later experience with an older patient, tortuosity of the artery was found to be a helpful pointer. After cannulation it is important to release the tourniquet before connecting the giving set, so that pulsatile flow may confirm that the artery and not a vein has been entered.

In a right-handed patient it is preferable to use the left radial artery in view of the possibility of damage due to ischæmia, although this appears to be small (Horton et al. 1953). In this patient the left forearm was encumbered by a splint for an intravenous drip, the preservation of which was considered vital. The right radial artery was therefore used, with no discernible ill consequence. The patient's grave state precluded her from being turned on to her side; hence, the intra-aortic route (Haxton 1952) was considered inadvisable.

I would now use blood alone for intra-arterial transfusion, in view of the arterial spasm attributed to fluids which utterly deprive the arterial wall of oxygen (Brown 1953).

The beneficial effect of nikethamide and the harmful effect of atropine, both dramatic, do not appear to me to be readily explained by the currently accepted pharmacology of these drugs.

Discussion

In the present case irreversibility was diagnosed early because of two associated clinical features following acute-on-chronic hæmorrhage: (1) the failure of rapid intravenous replacement of lost blood to restore the blood-pressure, or even to arrest or retard its precipitous fall, and (2) the feeble and evanescent pressor effect of noradrenaline. These are the essential ante-mortem features of irreversible shock (Wiggers 1943). It was because both these features were present that intra-arterial transfusion was thought to be indicated. Further intravenous transfusion seemed more likely to overload the circulation than to raise the blood-pressure—a prognosis which subsequent events supported.

Much has been learnt about irreversibility since the introduction of standard methods of producing irreversible shock in the laboratory (Wiggers and Werle 1942, Wiggers 1943). Prolonged hepatic hypoxia, with consequent peripheral vasodilatation, appears to be the dominant factor in the causation of irreversibility, and the maintenance or restoration of hepatic oxygenation prevents, or resuscitates from, experimental irreversible shock (Engel et al. 1944, Shorr et al. 1945, Frank et al. 1946, Seligman et al. 1947, Delorme 1951, Zanetti 1952, Wayne et al. 1954). Intra-arterial transfusion has also resuscitated from irreversible shock in a significant proportion of laboratory animals (Glasser and Page 1947, Wiggers 1949).

There is still controversy over the precise biochemical changes, consequent on prolonged anaerobic metabolism, which bring about the well-known phenomena of experimental irreversible shock (Granick 1951, Frank et al. 1952). Whatever the biochemistry, it is generally agreed that the change from reversible to irreversible shock is constantly associated with a change in the behaviour of the peripheral vasculature: reversibility by intravenous transfusion is associated with peripheral vasoconstriction, but the onset of irreversibility is preceded by vasodilatation. The total peripheral resistance is high in reversible shock and low in irreversible shock. The change from high to low peripheral resistance, from vasocontriction to vasodilatation, is postponed when hepatic oxygenation is maintained; in established irreversible shock restoration of hepatic oxygenation restores the peripheral resistance and the blood-pressure and resuscitates from irreversible shock (Wiggers 1943, Chambers et al. 1944, Shorr et al. 1945, Frank et al. 1946, Seligman et al. 1947, Glasser and Page 1946, Smythe et al. 1954, Wayne et al. 1954).

Hepatic blood-flow increases rapidly after intra-arterial transfusion (Griffith and Emery 1930, Johnson 1954). Initially the increase is due to direct perfusion by the transfused fluid (Glasser and Page 1948, Jones et al. 1950) via the hepatic artery in common with all the major branches of the aorta. The concept of a critical closing pressure affecting the renal and hepatic blood-vessels explains how these organs may be made ischæmic despite an apparently adequate perfusing pressure.

Hepatic vascular constriction is initiated by sympathetic vasomotor reflex (Griffith and Emery 1930), prolonged by a hormonal product of the partly ischæmic renal cortex (Shorr et al. 1945), and continued, when this has been exhausted, by the mechanical properties inherent in the structure of the vessel wall (Burton 1954). Among these properties is a paradoxical increase in distensibility of a collapsed arteriole. Intra-arterial transfusion, by a small direct increase in hydrostatic pressure within the aorta and its main branches, opens these collapsed vessels and makes way for arterial blood in a manner which intravenous transfusion cannot imitate even in favourable cases. In consequence the re-establishment of hepatic oxygenation inactivates a vasodepressor substance and elevates thereby the peripheral resistance and so the blood-pressure. The vicious spiral of hypotension is reversed.

In the light of this and other evidence it seems reasonable to suggest that the essential effect in irreversible shock of intra-arterial transfusion is the restoration of hepatic oxygenation.

From the standpoint of pure hæmodynamics it has been suggested that peripheral vasodilatation and reduction of peripheral resistance keep the blood-pressure low by diminishing the venous return and cardiac output (Shorr et al. 1945). In animals the peripheral resistance has been shown to affect the venous return and the cardiac output, and thereby to exert a disproportionate effect on the blood-pressure (Rashkind et al. 1953). In man, however, depression of the peripheral resistance has a variable effect on the cardiac output, which is increased more often than decreased. But the blood-pressure is lowered, even when the fractional decrease in total peripheral resistance is exactly balanced by the fractional increase in cardiac output (Shackman et al. 1954).

In man, therefore, changes in the total peripheral resistance have a disproportionately greater effect in altering the blood-pressure than have changes in cardiac output. Low blood-pressures are easily produced by sympatholytic techniques, regardless of any increased venous return and cardiac output.

All this suggests that, in irreversible shock, the dominating cause of the low blood-pressure and of the ineffectiveness of intravenous transfusion may be simply the great reduction in peripheral resistance and reactivity which follow long-continued hepatic anoxia.

This is not to imply that the cardiac output is actually normal, or that it can be raised as easily as usual, during shock. There is a reduction in cardiac output early in hæmorrhagic shock (Blalock 1940), which may well be due to diminished venous return through the liver. Eventually the heart loses its ability to react to a rising central venous pressure (characteristic of late irreversible shock) by increasing systolic output (Wiggers 1943). This is a late phenomenon, however, secondary to prolonged hypotension, whose dominating cause is some other factor (Wiggers 1943). It is possible, before this terminal phase, to increase the cardiac output during irreversible shock, but resuscitation is not thereby effected (Wiggers 1943). Thus, although poor coronary-artery perfusion and impairment of the force of myocardial contraction are important contributory factors to the hypotensive state and ultimately precipitate pulmonary œdema and death, heart-failure is a consequence of inability to raise the blood-pressure by intravenous transfusion and not its dominant cause (Wiggers 1943).

Previous reduction of the cardiac reserve, as from ischæmic heart-disease, will reduce the period of hypotension necessary to cause pulmonary œdema, and death may occur from this or from acute heart-failure even during the phase of vasoconstrictor shock; death alone is not pathognomonic of the precise syndrome called irreversible shock. Cerebral ischæmia and cerebral anoxia are the other common causes of death during reversible shock, and mishap may introduce these avoidable accidents into the list of immediate causes of death in irreversible shock. A clear airway and a head-down tilt are indispensable, and usually effective, in preventing these accidents.

The gradual development of heart-failure, which is the usual cause of death, accounts for the decrease in survival-time caused by intravenous transfusion in established irreversible shock. As might be expected, blood is worse than plasma in this respect, and both are worse than saline solution (Wayne et al. 1954).

A further consequence of this terminal heart-failure may be that sudden restoration of the peripheral resistance and blood-pressure at such a time, by intra-arterial transfusion, may overload the myocardium before it has had time to benefit from improved coronary perfusion. This would explain the fatalities which seem to have occurred in this fashion in a small proportion of the published cases. Even apart from this, simple overloading of the circulation may take place because of the small quantities of blood needed to initiate hepatic perfusion and to restore the peripheral resistance—as little as a fifth of the amount of blood withdrawn in order to produce chronic hypotension and irreversible shock (Glasser and Page 1946). Glasser and Page improved their survival-rates significantly by giving ouabain at the same time as an intra-arterial transfusion for irreversible shock.

Death may take place from intra-arterial transfusion for shock in patients with normal coronary arteries. It is therefore not surprising that for shock complicating coronary occlusion the results of intra-arterial transfusion are not strikingly successful (Berman and Akman 1952).

Before using any method which might raise the blood-pressure rapidly after a long period of severe hypotension, whatever the cause, there seems to be a strong case for rapid digitalisation with a safe and effective drug. I use intravenous strophanthin for this purpose.

It is apparent from the foregoing remarks that increasing coronary-artery perfusion for a few minutes by an intra-arterial transfusion cannot be a very important contribution to resuscitation from irreversible shock; for heart-failure is the consequence and not the cause of irreversibility. The effect of intra-arterial transfusion in restarting the stopped heart in animals and man (Crile and Dolley 1906, Negovsky 1945, Glasser and Page 1947) has perhaps focused undue attention on this particular property, which has been credited with an importance which cannot be deserved in resuscitation from irreversible shock. In exsanguination, on the other hand, which may produce acute coronary and medullary ischæmia, perfusion of the coronary and vertebral arteries is of obvious importance to the superiority of intra-arterial over intravenous transfusion (Glasser and Page 1948, Veal et al. 1952, Jones et al. 1950).

In all stages of shock renal-arterial perfusion (Glasser and Page 1948) and rapid restoration of urinary filtration (Jones et al. 1950) after intra-arterial transfusion must be of great advantage. In reversible shock intra-arterial transfusion is followed by reduction of a raised peripheral resistance, and rapid restoration of renal blood-flow may well be an important, possibly the most important, cause of this (Brown 1953, Shorr et al. 1945).

Although most of the foregoing observations have been made on laboratory animals, there is clinical and pathological evidence relating severe shock to hepatic anoxia in man. Thus the release of a portal-vein clamp is followed by a fall in blood-pressure related to the period of obstruction (Aird 1949), an effect also seen in animals (Selkurt 1954). In animals as well as in man necropsy has revealed centrilobular hepatic necrosis when death has been due to shock from various causes (Engel et al. 1944, Delorme 1951, Friedman et al. 1951, Anlyan et al. 1954, Bywaters 1946, Maegraith et al. 1947, Govan and MacGillivray 1950, Ellenberg and Osserman 1951).

Evidently oligæmia is only one of many factors contributing to the initiation and development of shock. All have been shown to interfere with renal and hepatic oxygenation in a manner consistent with the importance which the evidence suggests should be ascribed to these particular effects. There may yet prove to be a unified and coherent pathology of shock despite the many different ways in which it may be initiated.

Summary

A case-record is presented of resuscitation by intra-arterial transfusion from irreversible shock due to acute-on-chronic post-abortum hæmorrhage. This was rapidly effective after over 5 hours' profound shock following the failure of intravenous transfusion, the administration of noradrenaline and strophanthin, and the onset of an apparently terminal phase of shock with pulmonary œdema. Resuscitation was complete and permanent.

Evidence of the essential rôle of hepatic anoxia in the causation of irreversible shock is summarised. It is suggested that the restoration of hepatic oxygenation is the essential means whereby intra-arterial transfusion is effective in resuscitation from irreversible shock; and that the dominant disorder of function in irreversible shock is the great reduction of the peripheral vascular resistance consequent on hepatic anoxia.

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References continued at foot of next column

SEVERE POSTPARTUM HÆMORRHAGE ASSOCIATED WITH FIBRINOGEN DEFICIENCY

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POSTPARTUM hæmorrhage is one of the gravest emergencies in medicine. Its incidence and severity may be reduced by the use of oxytocics, and its danger has been lessened by the availability of stored blood for transfusion. In some cases, however, postpartum hæmorrhage is associated with defective clotting of the blood and may persist despite good retraction of the uterus. Fibrinogen deficiency is an important cause of defective blood-clotting in obstetric practice.

Reports on fibrinogen deficiency in obstetrics have been well surveyed by Barnett and Cussen (1954) and by Moore (1954). In the majority of the cases there was severe accidental antepartum hæmorrhage. A smaller number of cases has been reported in association with intra-uterine death of the fœtus due to rhesus antibodies (Reid et al. 1953). Reid et al. reported five cases of fibrinogen deficiency which they attributed to amniotic-fluid embolism. In four of these cases shock developed before delivery, with no evidence of antepartum hæmorrhage. After delivery the blood failed to clot, and in one case which was fatal many squamous cells were demonstrated in lung capillaries. The fifth case appears to have resembled the case described here. Reid and his colleagues postulated that in that case amniotic-fluid embolism had occurred because they found evidence of fibrinogen deficiency, but the patient is not reported to have shown signs of shock before the delivery.

The only other reports we have found of cases in which postpartum hæmorrhage was associated with fibrinogen deficiency, and with no other detectable abnormality, are those of Tagnon et al. (1946) and of Marchesi (1954). Both these cases were fatal.

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Case-report

The patient was a healthy woman, aged 29, a gravida 2 (the first pregnancy ended in miscarriage). The expected date of confinement was Dec. 16, 1954. Pregnancy was normal until the 36th week when slight hypertension developed. At 37 weeks the blood-pressure rose to 150/110 mm. Hg but fell to 130/80 mm. after treatment with reserpine (1 mg. daily) and rest in hospital for 8 days. On Dec. 10 at 39 weeks, her blood-pressure was 136/96 mm. Hg and she had œdema of the feet, so it was arranged to admit her on Dec. 11. From this time her story is as follows:

Dec. 11

4 A.M.—Spontaneous rupture of membranes and onset of labour pains. Uterine contractions strong and frequent. Pethidine 150 mg. and trichloroethylene were given.

8.30 A.M.—Cervix fully dilated. Contractions very strong and almost continuous.

8.35 A.M.—Fœtal-heart rate 80 per min. A general anæsthetic (nitrous oxide, oxygen, and ether) was given and forceps were applied.

9.5 A.M.—Easy low forceps delivery of a living male infant weighing 7 lb. 14 oz. (3572 g.). Ergometrine 0·5 mg. was injected intravenously during the birth of the shoulders.

9.8 A.M.—The placenta and membranes were expressed during the first contraction of the uterus after the injection of ergometrine. There was a brisk loss of approximately 20 oz. (540 ml.) following delivery of the placenta. 'Pitocin' 5 units injected intramuscularly. The uterus was massaged; it retracted well and the bleeding ceased. The placenta and membranes were inspected and appeared complete.

9.30 A.M.—Systolic blood-pressure only 80 mm. Hg. Blood taken for cross-matching and intravenous infusion of saline solution started.

10 A.M.—Pulse very rapid and of poor volume. Blood-transfusion commenced, 2 pints being given as quickly as possible. The uterus was found to be flaccid; it was massaged and a further 20 oz. (540 ml.) approximately was expressed. We did not notice whether this blood clotted.

10.30 A.M.—Under general anæsthesia the uterus was explored and found empty. It was firmly packed with gauze. Ergometrine 0·5 mg. injected intravenously.

11 A.M.—Blood-pressure not recordable. 3rd pint of blood commenced. Transfusion commenced in opposite arm with 1 pint (540 ml.) of glucose-saline solution containing 2 ml. of 1 in 1000 noradrenaline.

11.30 A.M.—Blood was oozing through the gauze pack. 4th pint of blood started. The uterine pack was removed and the uterus repacked very firmly with two rolls of gauze. The vagina was packed with cotton-wool pledgets rung out of weak 'Dettol' solution.

11.45 A.M.—The idea of hysterectomy was considered at this stage but was rejected because the uterus was well retracted, there was no external bleeding, and the patient was still extremely shocked. One of us (J. M. B. M.) then suggested the possibility of fibrinogen deficiency and took a sample of blood for clotting.

NOON.—The patient's blood had not clotted after 15 minutes. A supply of fibrinogen was requested and was dispatched from the National Blood Transfusion Depot at Leeds. 5th pint of blood started. 20 ml. of 10% calcium gluconate injected intravenously and 50 mg. of vitamin K intramuscularly.

12.30 P.M.—6th pint of blood started. Blood-pressure not recordable.

12.45 P.M.—Intra-arterial blood-transfusion started into the left radial artery. 2 pints was given quickly with dramatic improvement.

12.55 P.M.—Systolic blood-pressure 104 mm. Hg.

1.05 P.M.—Systolic blood-pressure 120 mm. Hg. 3rd pint of intra-arterial blood started. The uterus was well retracted but blood was beginning to ooze through the pack.

1.20 P.M.—Fibrinogen received from Leeds. 250 mg. injected intravenously.

1.25 P.M.—Bleeding ceased. Blood drawn for clotting showed a weak clot in 5 minutes and a firm clot in 9 minutes. The intra-arterial drip was continued slowly. (We have since learned that transfusions into the radial artery should be performed quickly and completed in an hour, owing to the risk of gangrene of the hand. Fortunately this complication did not occur.)

2.35 P.M.—Much improved. Blood clotted firmly in 4 minutes.

3.30 P.M.—Pulse 90 per min.; blood-pressure 130/90 mm. Hg. Intra-arterial drip discontinued. Penicillin and streptomycin were given prophylactically.

9 P.M. (12 hours after delivery).—The clotting power was tested, as it was intended to remove the uterine pack. Only a small clot formed after 5 minutes, and complete clotting did not occur. As no more fibrinogen was available until next day the pack was left in. Since delivery the patient had excreted only 6 oz. (171 ml.) of urine; this was heavily bloodstained.

Dec. 12

9 A.M.—280 mg. of fibrinogen injected intravenously. A sample of blood taken through the same needle immediately before the injection clotted firmly in 4 minutes. The uterine pack was removed without abnormal bleeding. The urine was now clear and there was a good output. The temperature rose to 100·6°F 24 hours after delivery, but was normal by the 3rd day.

Thereafter the puerperium was uneventful. On the 3rd day the hæmoglobin was 8·96 g. per 100 ml., and the level rose to 9·6 g. by the 10th day. Mother and baby were discharged well on the 12th day.

Discussion

This case exemplifies the danger of fibrinogen deficiency in an apparently uncomplicated case of postpartum hæmorrhage. Theoretically this deficiency could arise from failure of the liver to form fibrinogen, from precipitation of the fibrinogen by a thromboplastic substance, or from the using up of all the available fibrinogen in a hæmorrhage. We cannot say which of these was the cause in our case. Scott (1955) has suggested that fibrinogen deficiency may result from administration of dextran; but dextran had not been given in the present case. We gave only a small dose of fibrinogen as this was all that was available. Its efficacy confirms the observation by Barnett and Cussen (1954) that doses theoretically inadequate may be effective in practice.

In any case of postpartum hæmorrhage where the hæmorrhage persists despite an intact and well-retracted uterus, the simple "clot-observation test" (Weiner et al. 1953) or the more accurate test of Schneider (1952) should be performed. If the clotting power is impaired fibrinogen should be administered. As soon as adequate supplies are available a stock of fibrinogen should be kept in every large obstetric hospital.

The value of intra-arterial transfusion has been demonstrated in this case. Bingham (1952) regards this as the method of choice for treatment of severely shocked patients. It should be applied without delay if shock persists after blood has been given intravenously in a quantity calculated to restore the blood-volume.

Summary

A case is described of massive postpartum hæmorrhage, leading to profound shock, associated with fibrinogen deficiency. The hæmorrhage ceased after administration of fibrinogen by intravenous injection, and the shock responded to intra-arterial blood-transfusion.

We should like to express our appreciation to Dr. Brian Eastwood who gave the intra-arterial transfusion; to Dr. C. E. Wildeboer, the anæsthetist; to Dr. A. Clark, the house-surgeon; and to the midwifery staff. We are indebted to Mr. G. W. Theobald for permission to publish this report and for his advice and criticism.

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Reviews of Books

The Extra Pharmacopœia (Martindale)

23rd ed. London: Pharmaceutical Press. 1955. Vol. II. Pp. 1501. 57*s.* 6*d.*

"Martindale" goes from strength to strength. For more than seventy years it has enjoyed a position unique among works of reference common to pharmacists and physicians. Volume II, which completes this new edition, is more technical than volume I, which appeared three years ago.[1] However, only about a third of it deals directly with analytical addenda to the materia medica in the companion volume. Elsewhere there is a wealth of information and readable articles on such subjects as chromatographic analysis, ion-exchange resins, radiotherapy, radiant energy, nutrition, and hæmatology. Is the nomenclature of organic compounds a thorn in the flesh of the busy doctor? Let him settle the problem once and for all by spending an evening—maybe two evenings—on the appropriate chapter of Martindale. His appetite may then be whetted to attack the section on structure-action relationships.

Martindale remains invaluable as a source of references in abstract form, and as a starting-point for exploring the literature on a thousand and one topics of medical and pharmaceutical interest.

Surgery of the Sympathetic

A. LEE MCGREGOR, M.CH., F.R.C.S., consulting surgeon, Johannesburg General Hospital; honorary research associate, department of surgery, University of the Witwatersrand. Bristol: John Wright & Sons. 1955. Pp. 200. 30*s.*

Mr. Lee McGregor believes that the sympathetic nervous system is regarded by clinical students and by many practising surgeons and physicians as a *terra incognita*. He has therefore tried, in this small volume, to present simply and often diagrammatically the indications for, and the results to be expected from, operations on the autonomic system. The basic surgical anatomy and physiology is presented, together with a description of the standard operative procedures. No attempt is made to cover the whole field of peripheral vascular disease; for example, vessel-grafting and the clinical problems of peripheral embolism are not discussed.

It is essentially a book written by an applied anatomist, with liberal quotations from other authorities. Though it expresses many opinions with which individual angiologists would probably disagree, it should fulfil its purpose. There are many larger and more comprehensive books on the sympathetic nervous system, but none more readable.

Approach to Clinical Medicine

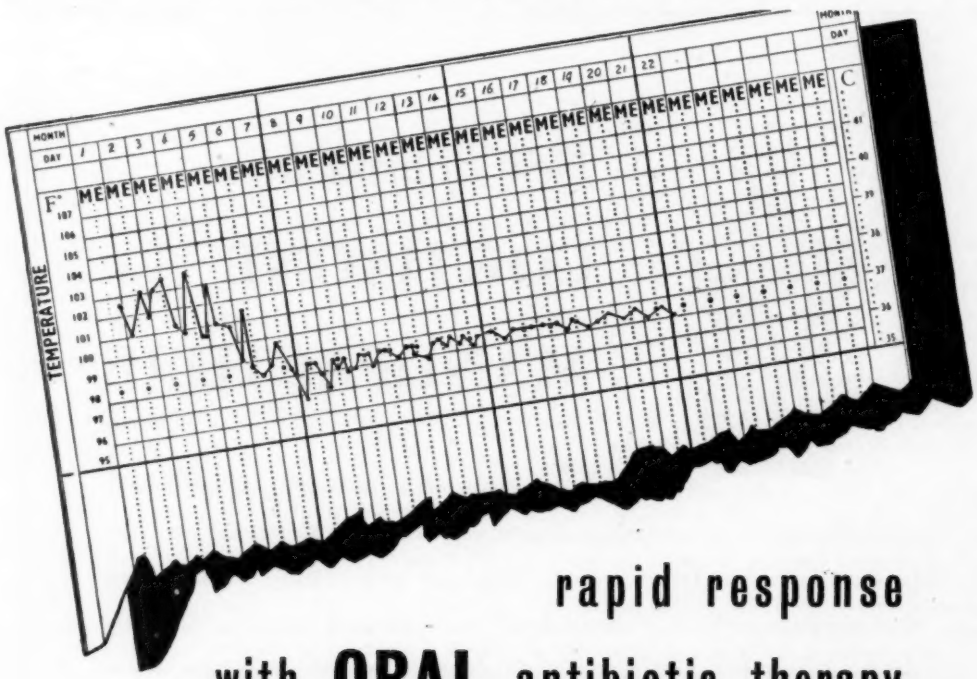
R. H. MICKS, F.R.C.P.I., King's professor of materia medica and pharmacy, University of Dublin; physician, Sir Patrick Dun's Hospital. London: J. & A. Churchill. 1955. Pp. 135. 8*s.* 6*d.*

IF the next generation of doctors are not good clinicians, trusting to clinical rather than laboratory observations, to themselves rather than to their *ancillæ*, it will not be for lack of wise advice. Professor Micks addresses himself to the first-year clinical student, showing him how to make good use of his opportunities, continually reminding him that he may soon be a practising doctor with dependent (but not uncritical) patients, and filling lacunæ in his more formal teaching. The book is lightly written, is full of common sense, and should do much to make "the rough places plain." There are a few surprises:

Immune serum is proposed for measles prophylaxis, but not gamma-globulin; and chloramphenicol, or a tetracycline, is described as useful for whooping-cough, without a caution. Poliomyelitis gets less space than typhus, and its respiratory paralysis "is invariably fatal unless the patient has artificial respiration through a tracheotomy tube carried out." Anxiety or mental conflict is not mentioned as a reason for complaint of fatigue. Surely rhinopharyngeal infection is a commoner cause of children's enlarged cervical glands than pediculi capitis, and can one be quite sure that more than one diarrhœic stool after the onset of pain excludes appendicitis?

But this is a good little book for the student's pocket.

1. See *Lancet*, 1952, ii. 617.



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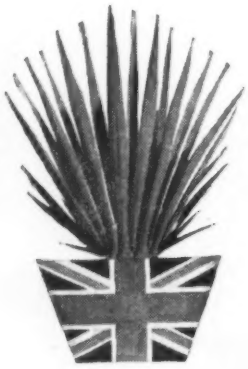

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THE LANCET
LONDON: SATURDAY, OCT. 1, 1955

Appetite and Hunger

IN the past few years some advance has been made in our knowledge of the causes of appetite and hunger; but it is still not possible to give a reasoned account of these common sensations, nor to apply rational treatment to some types of obesity and wasting. Hunger is appetite which has become disagreeable because satisfaction is unlikely or distant. Both sensations are obviously concerned with regulation of food intake, and in our civilised society they are extraordinarily complex reactions. It has often been remarked that man is the only animal which eats and drinks more than enough to meet his metabolic needs. Man's eating habits are conditioned somewhat by his social environment.[1] People may acquire the habit of eating too much because of their sociable natures; or conversely, feeling that their figures are not such as fashion requires, they may develop the habit of eating very little and in time suffer no sense of hunger. In minor psychological disturbances the amount of food eaten may be abnormal in one or the other direction. The Germans have a vivid term for the person who has troubles but compensates and stays happy by overeating—lard-sorrow. Thus, even in health appetite may vary greatly without necessarily giving rise to sensations of either hunger or satiety.

The problem is to find what factors cause or inhibit appetite, and how food intake and body-weight are regulated. Some who are in sound health appear to have a good appetite and yet remain thin; while others, equally active, do not seem to overeat and yet are heavy for their height. The popular belief is that the thin man "burns up his food more" (*luxus Konsumption*). PASSMORE and his colleagues in Edinburgh [2 3] have now shown that thin young men fed calories above their needs clearly absorbed all the food given, and that the subsequent small increase in calorie output could be accounted for by the specific dynamic action of the extra protein eaten. There was no evidence that they reacted to dietary excess by oxidising the surplus more efficiently than their fatter brethren. Yet these thin young men did not gain as much weight as might have been expected; they laid down protein and fat, but their body-water did not increase in proportion—that is, they responded to overfeeding by concentrating their tissues. The person who is underfed loses weight but not a corresponding amount of water; hence the appearance, if underfeeding is prolonged, of "isohydric" famine œdema, in which some of the water may be intracellular rather than extracellular. In the course of refeeding after starvation large amounts of nitrogen may be retained without a corresponding increase in body-weight. From these facts PASSMORE and his colleagues argue that cellular protein content may vary widely, and that at no point can it be said that an individual has normal protein nutrition simply because his cells contain a certain amount of protein. Thus, the thin young men stayed thin despite overfeeding because they concentrated their tissues in both fat and protein. It is hard to say what would have happened had the excess food been presented for a longer period. Probably they would have rejected it.

This prompts the question: Why reject food any more than eat it? Whence comes the desire for food or the feeling of satiety? Sensations from the stomach or duodenum are only a small part of the regulating mechanism. In an empty stomach vigorous hunger contractions appear, yet these cease before hunger and calorie requirements are satisfied; and hunger may be felt after gastrectomy or denervation of stomach and duodenum.[4] Hunger contractions are, as CARLSON [4] realised, probably only one manifestation of something more deep-seated. Another manifestation, in infants and animals, is restlessness, which has been interpreted as food-seeking activity. Obviously in the wild or primitive state motor activity was an essential preliminary to eating. Experiment shows that animals, such as rats, fit diet to energy needs with remarkable accuracy and speed. If presented with bulky food of small nutritive value they eat a greater volume than usual; if given a fortified diet they eat less.[4] Clearly the stomach is not the seat of the sense of satiety. In the one case the rats had fuller stomachs than normal, in the other case emptier. Man, too, in face of periods of quiet alternating with a few days of activity, automatically balances his food and energy output in the space of a day or two.[5] When it is remembered that the satisfaction of appetite involves locomotion, feeding reflexes, the recognition of food that is edible, and the unconscious recognition of food that satisfies the tissues, it is not surprising that a central coördinating mechanism has been found. This is apparently in the hypothalamus. Animals with lateral hypothalamic lesions may show both hyperphagia and unwillingness to work for their food [4]; in them normally linked activities have been dissociated. Also in the lateral hypothalamus lies an area whose bilateral destruction causes complete aphagia even in the presence of food. Slightly medial to this, bilateral lesions cause animals to wolf food and become grossly fat.[6] These two paired areas probably work in collaboration, each serving to inhibit or stimulate the other. The aphagia-inducing area is in just about the same position as a neural

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system, described by MAGOUN,[7] which determines not only whether other parts of the central nervous system become active, but also their level of activity. This bulbar facilitatory mechanism may be responsible for regulating the activity of the feeding reflexes—an idea borne out by the observation of SHERRINGTON [4] and CARLSON [4] that hunger is associated with generalised hyperactivity of the central nervous system. In addition, appetite and satiety are modulated by voluntary cerebral cortical impulses and by the many hormonic influences known to affect cellular activity.

Given that reflexes from the stomach are not essential to fire this central nervous mechanism to activity, a metabolite circulating in the blood may be responsible. Hypoglycæmia can cause contractions of the stomach, and this suggests that glucose may be the substance concerned. MAYER and his colleagues [8] have described considerable evidence supporting this suggestion. Yet it seems unlikely that glucose can be the main signal to the appetite centres. Diabetics feel hunger and may overeat (though it could be argued that here hormone imbalance has altered the threshold or response of the neurones). Furthermore, in short-term observations it was found that the desire for food was not altered by intravenous or intragastric administration of glucose half an hour before the main meal of the day.[9] Possibly proteins affect the eating centres directly or as a result of their metabolism. In a set of observations lasting three weeks it was found that a protein-rich diet had a far higher satiety value than a more calorie-rich one, and that there was no correlation between blood-glucose level and the sense of satiety.[10] The specific dynamic action of protein may be the factor involved. BROBECK [6] suggests that any increase in the total amount of heat in the body, acting through thermal gradients and thermal receptors, initiates impulses inhibiting the mechanisms responsible for feeding. An increase in environmental temperature would act in the same way: on this hypothesis food intake and temperature regulation are mutually interdependent.

Hypotheses such as this can explain rapid adjustments of food intake to energy demand, but not slower ones. After illness or operation a patient has little appetite and loses weight. During convalescence he makes up for this and returns to his previous condition.[5] Rats behave in the same way.[11] Similarly men in a primitive society who have been undernourished do not, in a more fortunate period, eat until they become overweight, but only until they return to normal.[12] WIDDOWSON [13] observed that Germans who had suffered long-continued undernourishment had not become stabilised at the low level, but when presented with unlimited food ate enough to provide 6000 calories a day and put on 10 kg. weight in eight weeks. There must, then, be slow-acting as well as fast-acting satiety receptors or factors. If PASSMORE's suggestion as to cell-protein content is correct, possibly the hypothalamic cells controlling food intake fire less vigorously when their protein level is high, and by being more labile than other cells forestall lack or excess in the tissues as a whole. This is speculation. Clearly, the central regulation of feeding depends on the integration of several different factors. In time it may be possible to devise specific treatment for centres causing abnormalities of appetite and body-weight.

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The Lungs in Mitral Stenosis

DISORDERED function and lesions of the lungs are a long-recognised feature of mitral stenosis, but only lately has the clinical importance of such changes been established. In 1936 PARKER and WEISS [1] found changes in the alveolar walls, and in the intrapulmonary arteries and arterioles, in patients with mitral stenosis. The alveolar walls showed œdema, thickening of the basement membranes, and sometimes conversion of the alveolar epithelium into thick cuboidal cells. The lumen of the pulmonary arterioles was reduced by medial muscular hypertrophy, often associated with intimal fibrous thickening and medial scarring. Necrotising arteriolitis was occasionally seen. Similar changes have been reported by other workers.[2–4] Since the original measurements of pulmonary-artery pressure in mitral stenosis,[5] pulmonary hypertension has been found to be an almost invariable complication of severe mitral stenosis. Indirect measurement of the left auricular pressure by wedging the cardiac catheter in a small branch of the pulmonary artery (pulmonary capillary venous pressure) [6] has enabled the pulmonary venous pressure and the pulmonary arteriolar resistance to be estimated. Slight pulmonary hypertension is secondary to increased left auricular pressure; but severe hypertension results from increased arteriolar resistance, which in turn is produced by a reduction in the lumen of the arterioles and small arteries. This reduction is sometimes due to the arteriolar changes already mentioned, but there is indirect evidence that reversible arteriolar constriction can occur. Thus BAYLISS et al.[4] showed that the pulmonary-artery pressure rose on exercise, without a parallel rise in cardiac output, in patients with severe mitral stenosis; and DAVIES et al.,[7] by administering hexamethonium, produced a fall in pulmonary-artery pressure, without a drop in cardiac output, in patients with severe hypertension. This suggests that the arteriolar constriction is reversible; and DAVIES et al. believe that the constriction may be mediated through the autonomic nervous system.

The radiographic changes in mitral stenosis have been well described by PARKINSON.[8] A notable feature is enlargement of the pulmonary arteries; and OLESEN,[9] in a follow-up study of 351 patients, noted that the hilar shadows were most prominent in patients with severe disease. Recently, changes in the lung-

1. Parker, F. jun., Weiss, S. *Amer. J. Path.* 1936, **12**, 573.
2. Larrabee, W. F., Parker, R. L., Edwards, J. E. *Proc. Mayo Clin.* 1949, **24**, 316.
3. Henry, E. W. *Brit. Heart J.* 1952, **14**, 406.
4. Bayliss, R. I. S., Etheridge, M. J., Hyman, A. L. *Lancet*, 1950, ii, 889.
5. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., Richards, D. W. jun. *J. clin. Invest.* 1946, **25**, 639.
6. Hellems, H. K., Haynes, F. W., Dexter, L. *J. appl. Physiol*, 1949, **2**, 24.
7. Davies, L. G., Goodwin, J. F., van Leuven, B. D. *Brit. Heart J.* 1954, **16**, 440.
8. Parkinson, J. *Lancet*, 1949, i, 895.
9. Olesen, K. H. Mitral Stenosis. Copenhagen, 1955. See *Lancet*, Aug. 13, 1955, p. 329.

fields have attracted interest. There are four main groups of abnormality: fine nodulation due to hæmosiderosis; fine horizontal striations in the costophrenic angles; changes in the small pulmonary arteries; and pulmonary œdema.

The systematic study of *hæmosiderosis* by LENDRUM et al.[10] led them to suggest that this condition resulted from multiple intrapulmonary hæmorrhages from varicose bronchopulmonary capillary anastomoses, with rupture into terminal bronchioles and the accumulation of foci of hæmosiderin. Opinions differ as to the association of hæmosiderosis with pulmonary hypertension. WOOD[11] found no correlation; but STEINER and GOODWIN[12] and GOODWIN et al.[13] found that it was generally associated with pulmonary hypertension, although pulmonary hypertension is so common in mitral stenosis that the association might be a chance one. Ossified pulmonary nodules have been described as a rare finding.[13 14]

Linear striations at the costophrenic angles have been noted by KERLEY[15] and others. These striations indicate that the mitral stenosis is severe and is associated with pulmonary vascular disease; gross pulmonary hypertension is usually present. The lines often vary with attacks of congestion. FLEISCHNER and REINER[16] ascribe them, when transient, to interlobular œdema; but KERLEY[15] and LEVIN[17] believe that they are due to engorged lymphatics. But they may be permanent, in which case they tend to be associated with hæmosiderosis and may be due to deposits of hæmosiderin in the septa. The lines sometimes disappear after successful valvotomy, but often persist along with other abnormalities in the lung.[13 16]

Abnormalities in the small pulmonary arteries in life were detected by GOODWIN et al.[18] These workers showed by venous angiocardiography that the arteries at the bases of the lungs were narrowed and irregular, in contrast to the enlargement of the main branches. The severity of the changes bore some direct relation to the height of the pulmonary arterial pressure. Selective pulmonary arteriography confirmed these changes, and DAVIES et al.[19] showed that the correlation between vascular change and pulmonary hypertension was close. They noted that the narrowing affected arteries with a predominantly muscular coat, while the large branches, which have relatively little muscle in their walls, were dilated. They also claimed that the arterial changes could be detected in plain radiographs, and the severity of the pulmonary hypertension gauged thereby, so that examination of a good plain radiograph of the chest was the best clinical guide to the level of the pulmonary arterial pressure. Narrowing never affected arteries in the upper lobe. The constriction must often be reversible, since post-mortem angiograms in cases where pulmonary hypertension and arterial abnormalities had been found in life showed far less constant narrowing, and organic changes in the arterioles were found only in a minority.[12] BÜLOW et al.[20] have also shown by angiocardiography narrowing of the lower-lobe arteries, commonly without organic disease of the arterioles as judged by lung biopsy. They took this to be further evidence of an initial functional constriction, but also found (as did DENST et al.[21]) that increased pulmonary vascular resistance was more usual in patients with structural arteriolar changes than in others. By contrast, GOODALE et al.[22] found no correlation between structural arteriolar changes and increased arteriolar resistance.

WOOD[11] reported frank *pulmonary œdema* in about 8% of his cases of significant mitral stenosis. It occurred chiefly in young women with a high pulmonary venous pressure, low arteriolar resistance, and mild pulmonary arterial hypertension. Attacks of paroxysmal dyspnœa, representing less severe pulmonary congestion, are more usual; and according to DAVIES et al.[7] these are no less common in patients with severe pulmonary arterial hypertension than in those with mild hypertension—suggesting that an increase in arterial pressure as well as in venous pressure may cause the attacks. Both WOOD[11] and GOODWIN et al.[13] agree that pulmonary œdema does not occur only in patients with the smallest valve orifices and most advanced disease of the mitral valve.

SHORT[23] and GOODWIN et al.[13] have found that the severity of the lung changes is directly related to the severity of the mitral stenosis in many, but not all, cases. Absence of the changes does not exclude a tight stenosis, but their presence virtually establishes it. Examination of a good plain film of the lungs in a case of mitral stenosis should therefore yield important information, although some clinicians may agree with BÜLOW et al.[20] that the arterial abnormalities are difficult to detect by straight radiography.

The lung changes after valvotomy have been studied radiographically by GOODWIN et al.,[13] who found that in a third of their patients who had a satisfactory clinical result the arterial abnormalities lessened and the horizontal lines disappeared. The disquieting persistence of abnormalities in the remaining two-thirds is in keeping with the recent studies by BISHOP et al.,[24] who showed that the pulmonary-artery pressure and arterjolar resistance do not always diminish after apparently successful valvotomy. The possibility that irreversible changes in the lung vessels may vitiate a technically satisfactory valvotomy should be considered, although GOODALE et al.[22] found that, if the valvotomy was adequate, pulmonary arteriolar resistance might fall significantly even in the presence of striking organic changes in the small pulmonary arterioles.

The mechanism responsible for narrowing of the pulmonary arteries and arterioles is unknown, but it seems probable that it is initiated by critical narrowing of the mitral valve and the consequent rise in pulmonary venous pressure. The teleological concept of arteriolar constriction as a shield protecting the lung capillaries from a powerfully acting right ventricle has been widely accepted[25 26] but has lately been challenged.[7] The organic changes in the walls of the arterioles have not been satisfactorily explained. The arteriolar necrosis found in some cases closely resembles the lesions in malignant systemic hypertension; and SYMMERS[27] has suggested that the pulmonary arteriolar disease may be the result of prolonged and severe

10. Lendrum, A. C., Scott, L. D. W., Park, S. D. S. *Quart. J. Med.* 1950, **19**, 249.
11. Wood, P. *Brit. med. J.* 1954, i, 1051, 1113.
12. Steiner, R. E., Goodwin, J. F. *J. Fac. Radiol., Lond.* 1954, **5**, 167.
13. Goodwin, J. F., Hunter, J. D., Cleland, W. P., Davies, L. G., Steiner, R. E. *Brit. med. J.* Sept. 3, 1955, p. 573.
14. Elkeles, A. *Proc. R. Soc. Med.* 1947, **40**, 405.
15. Kerley, P. *In* Textbook of X-ray Diagnosis. Edited by S. C. Shanks and P. Kerley. London, 1951.
16. Fleischner, F. G., Reiner, L. *New Engl. J. Med.* 1954, **250**, 900.
17. Levin, B. *Amer. Heart J.* 1955, **49**, 521.
18. Goodwin, J. F., Steiner, R. E., Lowe, K. G. *J. Fac. Radiol., Lond.* 1952, **4**, 21.
19. Davies, L. G., Goodwin, J. F., Steiner, R. E., van Leuven, B. D. *Brit. Heart J.* 1953, **15**, 393.
20. Bülow, K., Biörck, G., Axen, O., Krook, H., Wulff, H. B., Winblad, S. *Amer. Heart J.* 1955, **50**, 242.
21. Denst, J., Edwards, A., Neubuerger, K. T., Blount, S. G. jun. *Ibid*, 1954, **48**, 506.
22. Goodale, F., Sanchez, G., Friedlich, A. L., Scannell, J. G., Myers, G. S. *New Engl. J. Med.* 1955, **252**, 979.
23. Short, D. S. *Brit. Heart J.* 1955, **17**, 33.
24. Bishop, J. M., Donald, K. W., Wade, O. L. *Clin. Sci.* 1955, **14**, 329.
25. Lewis, B. M., Gorlin, R., Housesay, H. E. J., Haynes, F. W. Dexter, L. *Amer. Heart J.* 1952, **43**, 2.
26. Wood, P. *Brit. med. Bull.* 1952, **8**, 348.
27. Symmers, W. St C. *J. clin. Path.* 1952, **5**, 36.

pulmonary hypertension. ENTICKNAP [28] found that arteriolar sclerosis in the lungs was not always preceded by capillary dilatation, and he suggested that the organic arteriolar changes depended on pulmonary arterial, rather than venous, hypertension. But absence of hyalinisation (which characterises the systemic arterial lesions produced by hypertension) in all his cases led ENTICKNAP to postulate that pulmonary and systemic arterioles might differ fundamentally. In 4 of his cases thrombi were found in the arterioles, and these thrombi might have accounted for the sclerosis. Possibly repeated thromboses or thrombo-embolism may account partly for the arteriolar changes, but conclusive proof is lacking. Rheumatic arteritis in the main pulmonary arteries, and occasionally in the smaller branches, has been reported,[29 30] but this is unlikely to play any important part in bringing about arteriolar sclerosis or pulmonary hypertension.[20 31]

Scalpel in the Surgery?

THE amount of minor surgery met with in general practice may vary a little, according to the type of practice and the kind of industries in the locality; but the attitude of the practitioner to its performance varies very widely. To some it is a skill to be developed and increased, while to others it is a time-consuming hindrance to the proper work of the day.

Perhaps not very long ago the practitioner of today was himself a final-year student or a houseman taking his part in the busy routine of casualty and surgical outpatients, gaining experience and judgment as well as dexterity in the lesser surgical procedures left to him by colleagues whose eyes were on higher planes of surgical achievement. The sebaceous cyst, the circumcision, the localised abscess —these opportunities are met with often enough in general practice to encourage any practitioner who wants to maintain his skill and to gain the added satisfaction of seeing his own patient through yet one more clinical adventure. In the country-town practice (where there is an operating-theatre at the cottage hospital), in the few prototype health centres, and in a few group-practice units, there may be "minor ops" theatres equipped to a standard of efficiency that the single-handed practitioner cannot achieve. In urban practice, however, where group practices are less common, practitioners will undertake their own minor operations less often. As the items of service making up a day can usually be rearranged to enable a desired object to be achieved, we must presume that it is not simply the lack of time that discourages such work, but a combination of factors including inadequacy of premises (a satisfactory examination room is not necessarily a good theatre), difficulty in getting the help of an anæsthetist, absence of a recovery room, and often lack of the trained nursing help which makes the maintenance of strict surgical sterility practicable. For such reasons many family doctors, though well able to do their own minor surgery competently, refer their patients to the casualty department of their local hospital. They know that the operation will be performed there in technically satisfactory circumstances, though the attendance may be a considerable inconvenience to the patient and the operation a nuisance to the casualty officer.

In the valuable article which we publish this week, Dr. J. H. HUNT develops a principle which, if applied in the larger hospitals, might resolve the difficulty to the advantage of both hospital and practitioner. It should not be impossible to establish, at hospitals with large casualty departments, a minor-operations theatre where visiting general practitioners could do their own minor surgery. Such a department could be efficiently staffed and equipped, and the services of an anæsthetist should be easily forthcoming. Local circumstances would determine whether all the work of a department such as this would be done by doctors on their own patients, or whether, as Dr. HUNT suggests, a "general-practitioner specialist" should be appointed on a sessional basis. Either way, the casualty officer would be relieved of much non-casualty work which he may find hard to fit into a programme not designed for it.

There are all too few links between the large hospital and the general practices that feed it, and if this one were to be forged it might do great good. It is in casualty that the young hospital resident sees what he takes to be examples of the inefficiency and ineptitude of the family doctor. It would be better for him if he were taught his minor surgery by a competent general practitioner who could give him an understanding of the background to whatever surgical procedure is undertaken.

28. Enticknap, J. B. *Ibid*, 1953, **6**, 84.
29. Kugel, M. A., Epstein, E. J. *Arch. Path. (Lab. Med.)* 1928, **6**, 247.
30. Gross, L. *Amer. J. Path.* 1935, **11**, 631.
31. Friedberg, C. K. Diseases of the Heart. Philadelphia, 1949.

Annotations

TRIUMPHS FOR CHEMISTS

Two notable pieces of chemical research have been announced that are of direct interest to medical men. The first of these (as already noted briefly in these columns [1]) is the elucidation of the structure of the molecule of vitamin B_{12}, or cyanocobalamin as it is officially named. Isolated and introduced to medicine seven years ago, vitamin B_{12} is exceptional among biological substances of importance in human nutrition because it contains cobalt. It is now well known that the vitamin is essential for the proper development of erythroblasts, and the commonest disease in this country with which it is connected is pernicious anæmia. In this disease the vitamin is not absorbed, and the anæmia is relieved by administering the vitamin parenterally in very small doses, measured in microgrammes.

The elucidation of the chemical nature of vitamin B_{12} has resulted from a combination of crystallographic work at Oxford, calculation at Los Angeles, and chemical studies at Cambridge and the Glaxo Laboratories at Greenford, Middlesex. The crystallographic part was carried out by Dorothy Hodgkin and her colleagues.[2] To the uninitiated some of the diagrams that illustrate their paper look like maps of London's Underground, and others appear to belong to space fiction. We are not surprised to learn that Dr. Hodgkin and her colleagues at Oxford had to call in Californian cybernetic assistance in the shape of SWAC (National Bureau of Standards western automatic computer) to help them with their calculations. The formula they eventually proposed was complex and represents a considerable achievement for

1. *Lancet*, Aug. 20, 1955, p. 402.
2. Hodgkin, D. C., Pickworth, J., Robertson, J. H., Trueblood, K. N., Prosen, R. J. *Nature, Lond.* 1955, **176**, 325.

crystallography. "To be able to write down a chemical structure very largely from purely crystallographic evidence on the arrangement of atoms in space—and the chemical structure of a quite formidably large molecule at that—is," they say, "for any crystallographer something of a dream-like situation." The crystallographic data by themselves left a number of points in doubt, and these have been tested and largely resolved by the workers at Cambridge and Greenford,[3] who used regular chemical methods. An interesting feature of the molecule of vitamin B_{12} ($C_{63}H_{90}O_{14}N_{14}PCo$) is the cyclic grouping round the cobalt atom, which is that present in the porphyrins.

The second chemical triumph is the determination of the structure of the insulin molecule. Insulin proved a much harder problem than vitamin B_{12}, and ten years have elapsed since Sanger and his colleagues at Cambridge published their first paper on this subject. The details now described by Sanger et al.[4] show that, compared to vitamin B_{12}, insulin has an enormous molecule with the empirical formula $C_{254}H_{377}O_{75}N_{65}S_6$, giving a molecular weight of 5733·5. The structure of the molecule consists of two parallel straight polypeptide chains linked by sulphur bridges that are parts of cystine residues. These two polypeptide chains are not, as might be expected, equal in length; the upper chain contains 21 units and the lower chain 30 units (counting each cystine residue as 2 cysteine units); so the insulin molecule must be askew in some manner, possibly coiled. Analysis of the amino-acids present in the molecule showed that leucine occurs most frequently at six times, valine five times, glutamic acid, glycine, and tyrosine four times, aspargine, alanine, cystine, glutamine, phenylalanine, and serine are represented three times, histidine twice, and arginine, lysine, proline, and threonine only once. Notable absentees are methionine and tryptophane. The exact arrangement of these amino-acids in the two parallel chains has been worked out in detail by Sanger and his colleagues—a very striking piece of chemical detective work. The Cambridge group have also shown [5] that there are small differences in the composition of the polypeptide chains of the insulins of different species; cattle, pig, and sheep insulins differ from each other in this way.

The elucidation of the structure of insulin and vitamin B_{12} may point the way to their eventual synthesis. The supply of cortisone has depended on chemical knowledge of the structure of the drug and its partial synthesis. But for both vitamin B_{12} and insulin we have efficient biological sources, the use of which has been brought to a high degree of perfection. Moreover these substances are produced remarkably inexpensively. A diabetic patient on 40 units of insulin zinc suspension daily uses about 7 pennyworth of insulin; while for the patient with pernicious anæmia on 100 μg. vitamin B_{12} weekly the cost is about 10*d*. (the streptomyces that produces the vitamin is a notably efficient organic chemist). The posterior-pituitary hormones, oxytocin and vasopressin, and at least one of the anterior-pituitary hormones have known chemical structures and have already been synthesised by American workers, but the methods of synthesis are not at present suitable for large-scale production. Yet even if knowledge of structure does not affect the supply of material for treatment, it is very important. We hope that fundamental information of this sort will help us to understand the mode of action of insulin, vitamin B_{12}, and the others; it may lead to better treatment and even aid prevention in the long run. Doctors will watch with unsimulated interest the results of the efforts of their chemical colleagues, even though they may not follow the technical details.

3. Bonnett, R., Cannon, J. R., Johnson, A. W., Sutherland, I., Todd, A. R., Smith, E. L. *Ibid*, p. 328.
4. Ryle, A. P., Sanger, F., Smith, L. F., Kitai, R. *Biochem. J.* 1955, **60**, 541.
5. Brown, H., Sanger, F., Kitai, R. *Ibid*, p. 556.

SYNTHETIC ARTERIAL GRAFTS

FOR forty years arterial surgery stood where this century's early pioneers had left it. Only by local repair was it possible to reconstruct a major artery. Grafting with a segment of vein, though occasionally successful, never became a standard method of bridging the longer defects. In 1949 Gross and his colleagues [1] described the clinical application of Carrel's method of homografting with the stored arteries of another individual. Since then surgeons all over the world have followed this lead, and major arterial lesions up to and including the aortic arch can now be excised and the artery reconstructed. Such arterial segments are usually dead when implanted, and they do not retain their original structure for long afterwards. Within a few weeks only extracellular material (mainly the elastic layers) remains. The main virtue of the arterial homograft, apart from its smooth lining and elasticity, seems to lie in its negative features—its inertness and the mildness of the reaction that it evokes, confined to a slow, healing incorporation which secures its function as a major blood-vessel.

Human arterial grafts are scarce. Even with permanent storage, such as is now possible with deep-freezing [2] and freeze-drying,[3] the essential difficulty of procuring the grafts remains. Other forms of prosthesis have been tried. Intubation of the arterial defect by rigid protheses of metal, glass, or plastic nearly always leads to hæmorrhage or thrombosis, though Hufnagel and his colleagues [4] have shown that in the thoracic aorta of man and the dog a polished 'Perspex' tube or ball-valve will usually remain patent if fixed by a multi-pointed nylon ring at either end. Below this level, and particularly where the soft tissues are mobile, all methods involving rigid tubes may be expected to fail. A much more promising method was introduced by Voorhees et al.[5] They fashioned tubes of a plastic cloth, 'Vinyon N,' and sutured these into the dog's abdominal aorta. The results encouraged them to use the same method in patients urgently needing operation, and in 1954 they reported good results after grafting with this material in 18 patients, mostly with abdominal aneurysms.[6]

The technique of inserting cloth tubes is much the same as that of homografting. When the arterial clamps are released blood leaks between the interstices of the fabric. The amount of bleeding depends on the material used, its weave, and its water-repellancy. Vinyon N is less satisfactory in this respect than finer fabrics such as 'Orlon,' 'Dacron' ('Terylene'), and nylon. It generally needs to be "pre-clotted" by preliminary exposure to whole blood, either in vitro or by prolonging the interval between removal of the distal clamp and removal of the proximal clamp. A liberal amount of enmeshed fibrin is helpful in that it provides a medium for the migration of fibroblasts, which organise the prosthesis into a living fibrous tube with a durable cloth reinforcement. This would seem to be an excellent substitute for a homograft: in fact it may prove in some ways even better, for homografts may have a limited life. Degenerative changes have already been reported in early dog preparations,[7] but there are so far no reports of late failure in cases grafted with suitable material by established methods. Arterial grafts have now been applied in several hundred cases, some as long ago as 1948. At St. Mary's Hospital, London, alone over 100 such grafts have now been applied, 40 of them to the aorta. Most of these were

1. Gross, R. E., Bill, A. H., Peirce, E. C. *Surg. Gynec. Obstet.* 1949, **88**, 689.
2. Eastcott, H. H. G., Hufnagel, C. A. *Surg. Forum*, 1950, p. 269.
3. Marrangoni, A. G., Cecchini, L. P. *Ann. Surg.* 1951, **134**, 977.
4. Hufnagel, C. A., Rabil, P., Harvey, W. P., McDermott, T. F. *Surgery*, 1954, **35**, 673.
5. Voorhees, A. B., Jaretski, A., Blakemore, A. H. *Ann. Surg.* 1952, **135**, 332.
6. Blakemore, A. H., Voorhees, A. B. *Ibid*, 1954, **140**, 324.
7. Coleman, C. C. jun., Deterling, R. A. jun., Parshley, M. S. *Surgery*, 1955, **37**, 64.

frozen or freeze-dried homografts, but synthetic tubes are now increasingly used for all but the smaller vessels.

Much research is going on in the U.S.A. with the object of finding the most suitable synthetic arterial grafts, and 1955 has brought a rich harvest of information.[8] Hufnagel and Rabil [9] have now been using orlon (an acrilo-nitrile polymer mostly used for shirts) long enough to have great confidence in its properties as a graft material. Cloth bifurcations, made like a pair of trousers but with an outside French seam, have been inserted in 15 cases after resection of the aortic bifurcation, without hæmorrhage or thrombosis. Orlon has only the slightest tendency to early leakage; it can be sterilised by autoclaving; and it does not fray or separate at the arterial suture line. Hufnagel has also used braided, seamless, orlon tubes, which are preferable to the sewn-up type for vessels smaller than the common iliac artery. Braided nylon, made up by a commercial shoe-lace manufacturer to 1/4-in. internal diameter, was used in an experimental study by Edwards and Tapp.[10] Coating the cloth with silicone was found to prevent early leakage, while a unique flexibility could be conferred on these narrow grafts by a crimping or corrugating process (heating with the tube longitudinally compressed), thus producing a material resembling the tubing from a gas mask or anæsthetic apparatus. Surprisingly, these irregular grafts functioned well when implanted into the abdominal aorta of small dogs. Shumacker and King [11] have tried heat-sealing the mesh of a nylon cloth with a layer of polythene sheeting, but this may have the disadvantage of greatly reducing the fibroblastic invasion. Poth [12] also considers it unwise to rely on a single layer of cloth. Multiple layers, he believes, are safer; but they should be added after the luminal portion has been inserted, since otherwise blood-clots may accumulate between the coats as in a dissecting aneurysm.

An ingenious method has been devised in Minneapolis, where Shumway et al. [13] have been using thin strips of polyvinyl sponge, wrapped round a tool of the desired size and shape, and boiled. This material becomes flattened on its lining surface, and wholly integrated, on cooling, to form a resilient, tough graft which somewhat resembles an actual artery. Experimental operations have been successfully completed, but no-one yet has much clinical experience of such grafts.

The advantages of ready-made or quickly tailored cloth grafts for arteries are impressive. In future they should be no more difficult to obtain than suture material or bone-plates. Rob and Eastcott [14] have described their successful use in the treatment of mycotic aneurysm, a condition hitherto irremediable by reconstructive surgery; a homograft would almost certainly have failed owing to sloughing. In at least one other respect cloth grafts are better than homografts in the treatment of aortic aneurysms: the "normal" vessel beyond the sac is often much wider than any normal homograft, and synthetic grafts can be made to measure, using the aortogram as the pattern. It now remains to explore the possibility of using smaller, seamless grafts, and bifurcating grafts, in the more peripheral arteries, and to ensure that whichever pattern proves best is manufactured to a high standard and is widely distributed. The general surgeon must also familiarise himself with the technique of inserting them, so that in emergency this new surgical manœuvre can be applied to any patient who urgently needs it.

8. Deterling, R. A., Bhonslay, S. B. *Ibid*, 1955, **38**, 71.
9. Hufnagel, C. A., Rabil, P. *Arch. Surg., Chicago*, 1955, **70**, 105.
10. Edwards, W. S., Tapp, J. S. *Surgery*, 1955, **38**, 61.
11. Shumacker, H. B., King, H. *Surg. Gynec. Obstet.* 1954, **99**, 287.
12. Poth, E. J. *Surgery*, 1955, **38**, 90.
13. Shumway, N. E., Gliedman, M. L., Lewis, F. J. *Surg. Gynec. Obstet.* 1955, **100**, 703.
14. Rob, C. G., Eastcott, H. H. G. *Brit. med. J.* 1955, i, 378.

VITAMIN D AND A.T.10

VITAMIN D is formed when ergosterol or 7-dehydrocholesterol are exposed to ultraviolet light. Ergosterol, from plants such as ergot, is converted to vitamin D_2, which has been named ergocalciferol but is better known as calciferol. 7-dehydrocholesterol, found in animals, is converted to vitamin D_3, or cholecalciferol, and this is the compound produced when animals are exposed to sunlight; it is the vitamin D of fish-liver oils. What was known as vitamin D_1 was found to be a mixture of sterols, and the term has been abandoned. Among the substances formed when ergosterol is irradiated, only one other is important in medicine: dihydrotachysterol or 'A.T.10' (antitetanic preparation no. 10).

The principal effect of vitamin D is to promote the absorption of calcium from the gut,[1] and for this function it is essential.[2] Without the vitamin animals get rickets or osteomalacia through lack of calcium, and with the vitamin rickets is cured. Occasionally patients have rickets because they are resistant to vitamin D and they need very large doses to enable them to absorb calcium.[3] Resistance to the vitamin may appear in the course of the treatment of osteomalacia.[4] Other effects of vitamin D become apparent with large doses: in particular, as well as increased absorption of calcium, a rise in the serum-calcium to abnormally high levels and an increased loss of calcium and of phosphate in the urine. These effects resemble those of parathormone, and they are best studied in patients or animals deprived of their parathyroid glands.[1] They cannot usually be demonstrated in animals deprived of vitamin D.[5] A.T.10 resembles vitamin D in its action on the intestinal absorption of calcium; but, according to Albright and his associates, the parathormone-like effects on urinary excretion are more pronounced than with vitamin D.[6]

In man (but not in the chick) vitamins D_2 and D_3 are equally potent, and it has until now been entirely a matter of convenience which of these two was given to a patient. A.T.10 has on the whole been reserved for patients with hypoparathyroidism; but in this disorder it is now given less often than formerly, since it is expensive and calciferol is easily available and generally effective because of the parathormone-like effects of large doses.

Early reports from Germany suggested that A.T.10 did not cure rickets,[6] and Albright et al.[7] also came to this conclusion; but Shohl and his associates [8 9] showed that it could do so. Liu and Chu [4] made the remarkable observation, in 5 cases of renal osteodystrophy, that A.T.10 increased the intestinal absorption of calcium and that the calcium was retained in the body; vitamin D did not increase the absorption of calcium in these patients. Recently Saville et al.[10] have found that A.T.10 maintained a satisfactory retention of calcium in 6 patients with rickets resistant to vitamin D. They argue that the actions of A.T.10 do not differ from those of calciferol; but, except in 1 patient, they did not compare the two substances directly. Nevertheless it seems that, in these patients at least, A.T.10 mimicked the actions of large doses of vitamin D. This is important in view of the discovery reported by Dr. Dent and his associates on p. 687 of this issue. In treating the tetany of patients deprived of their parathyroid glands, Dent

1. Albright, F., Sulkowitch, H. W. *J. clin. Invest.* 1938, **17**, 305.
2. Walker, A. R. P. *Amer. J. clin. Nutr.* 1955, **3**, 114.
3. Albright, F., Butler, A. M., Bloomberg, E. *Amer. J. Dis. Child.* 1937, **54**, 529.
4. Liu, S. H., Chu, H. L. *Medicine, Baltimore*, 1943, **22**, 103.
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et al. found, as others have done, that some became quite insensitive to all the actions of vitamin D_2 and remained so even when the dose which had previously maintained them well was greatly increased. When these patients had their treatment changed to vitamin D_3 or A.T.10 their response was again entirely normal.

This finding has no parallel, and it raises many exciting possibilities. It is of course of immediate practical importance in the management of patients with parathyroid tetany which has become refractory to other treatment. In addition, it may have a bearing on the pathogenesis and treatment of rickets resistant to vitamin D.

OPERATIVE TECHNIQUES FOR LARGE-BOWEL GROWTHS

BECAUSE carcinoma of the large bowel can sometimes be cured by an effective operation the finer points in technique are important. Shallow et al.[1] found a five-year survival-rate of 70% after removal of localised carcinoma in the rectal and rectosigmoid area. This suggests that if the growth and its areas of spread can be encompassed all should be well—provided that operative manipulation does not encourage embolic metastases or local recurrence. After resection, recurrence at the suture line may be due either to inadequate excision or to implantation of desquamated malignant cells from the bowel lumen. Cole[2] thinks that inadequate excision is an unlikely cause since recurrence rarely arises at a colostomy after excision of a rectosigmoid growth, but is common after resection and anastomosis for such lesions, even though the amount of bowel removed at resection may be no less than that excised at abdominoperineal excision. This argument is, however, weak since excision of a rectosigmoid growth prior to anastomosis is liable to be inadequate on the distal and not the proximal side; the evidence of immunity of a colostomy to recurrence has therefore little bearing on the matter. Nevertheless the possibility that implantation may sometimes be the cause is supported by the experimental work of Vink.[3] In rabbits the colon was transected and anastomosed 4 cm. distal to a site where a suspension of the Brown-Pearce tumour had previously been injected into the bowel lumen. Vink showed that implantation occurred in any areas contaminated with luminal contents, and further that the suture line was more prone to implantation after disinfection of the bowel by sulphaguanidine and streptomycin. The Brown-Pearce tumour may be more avid than a carcinoma in man's large bowel. Certainly there is no evidence to suggest that carcinoma in man seeds itself in the mucosa at lower levels in the bowel. The Brown-Pearce tumour may not do so either, but Vink conducted no control experiments with injection alone to prove this. He rightly draws attention to the danger of applying his results to human pathology. Nevertheless, when resecting carcinoma of the large bowel it is wise to follow Cole's technique by placing ligatures around the gut above and below the lesion before mobilisation, in order to minimise the risk of contaminating with exfoliated cells the site destined for suture.

The main problem in encompassing growth is removal of lymph-glands. Here there are two difficult questions: which glands are involved, and are some glands hidden from sight? It is common knowledge that glandular enlargement may be due simply to inflammation; and, as Wood and Wilkie[4] observed, the presence of enlarged glands should in itself be no deterrent to a curative excision or resection. Blatt and Cincotti[5] have made the converse observation of lymph-nodes which appear normal but contain microscopic carcinoma. A partial solution is to remove every lymph-gland within sight. But not every gland is easily visible; some are hidden in pelvic or mesenteric fat. So Blatt and Cincotti suggest that vital dye be injected to make the glands abundantly clear to the surgeon's eye. Basing their technique on the experience of Wood and Wilkie they inject Evans-blue into the submucosa of the rectum below Houston's lowermost valve; this stains not only mesenteric but also hypogastric and common iliac glands, and sometimes the para-aortic group. This injection affects the glands throughout the pelvis; and thus the technique is applicable to growths of bladder, cervix, and uterus as well as of rectum. There is one defect: malignant cells do not take up the dye; so any gland replaced by growth remains unstained.

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HÆMOPHILIA

HÆMOPHILIA is not a common condition—the prevalence in males in this country is estimated at 1–2 per 100,000—but it gives rise to a "pressing social problem." Four years ago the Medical Research Council set up a Hæmophilia Committee, under the chairmanship of Dr. J. F. Wilkinson, which made two recommendations: one was that a number of clinics and laboratories should be invited to act as reference centres using uniform diagnostic methods and coördinating information; the second was that a memorandum should be prepared to give a succinct account of modern views on the diagnosis and treatment of blood-clotting disorders, and details of the techniques recommended. The first of these recommendations has already been acted on; and the second is now carried into effect by the publication of a M.R.C. monograph.[1] The monograph, by Dr. R. G. Macfarlane and Dr. Rosemary Biggs, is a remarkable feat of compression and clarity. The emphasis is on the laboratory investigation of blood-clotting disorders, and full practical details are given of the recommended tests, from simple whole-blood clotting to the thromboplastin-generation test. The practising pathologist will sigh a little over perfectionist recommendations such as "accept only samples in which no technical difficulties were encountered in obtaining the blood"; and, if he has any experience of these tests, he will know that the short descriptions refer to tests that can take a long time to arrange and need skill and practice for reliable results. The laboratory section is preceded by a section on the clinical diagnosis of hæmophilia and its differentiation from the purpuras; and there is a short and sensible section on the treatment of hæmophilia and related clotting defects, the management of bleeding from special sites, and dental extraction. Everyone working in this field will want a copy of the monograph for the bookshelf or the bench.

IN THE NUFFIELD TRADITION

AT the annual dinner of the Royal College of Obstetricians and Gynæcologists, on Sept. 23, Sir Arthur Gemmell, the president, announced a munificent gift from Lord Nuffield towards the college's building fund. Through the Nuffield Provincial Hospitals Trust, Lord Nuffield has given £50,000, and to this he has added from his private resources a further £75,000. In acknowledging the gift Sir Arthur said that the council proposed to associate Lord Nuffield's name with the new building,[2] which would be known as the Royal College of Obstetricians and Gynæcologists, Nuffield College, Regent's Park. In all £400,000 would be needed for the building. The move from the gentle shelter of Queen Anne's Street to the park of the more robust Prince Regent is surely a sign of the college's expanding interests and authority, and all will wish the fellows and members many fruitful years in their new home to which Lord Nuffield has made such a notable contribution.

1. The Diagnosis and Treatment of Hæmophilia and its Related Conditions. Medical Research Council memorandum no. 32. H.M. Stationery Office. 1955. Pp. 23. 2s. 6d.
2. See *Lancet*, 1954, ii, 182.

Special Articles

MEDICINE AND ADMINISTRATION*

Sir RUSSELL BRAIN
Bt., D.M., P.R.C.P.

THIS occasion enables me to express the gratitude of the medical profession to the members of a hospital management committee, and thus, indirectly, to all hospital management committees, for the self-sacrificing and time-consuming work which they do for the benefit of the Health Service.

It seems to me rather a happy paradox that the National Health Service should require as much voluntary service as the old voluntary hospital system, if not more. This has advantages which I think we are sometimes in danger of losing sight of. I am sure it is a good thing that, at a time when we are all sensitive to the dangers of excessive central control, a considerable degree of responsibility for the management of our hospitals should rest upon people who, although they may be appointed by the Minister or by regional hospital boards, are essentially—I hesitate to say ordinary people!—but representatives of ordinary people, to whom this kind of public service appeals, who have local knowledge, and who are prepared to give up the time to it. And, of course, you represent the public also as patients; for we are all, unless we are very exceptional people indeed, from time to time patients, and in the Health Service the patient is what is called, in economic jargon, the consumer. But I am not forgetful of the fact that some members of hospital management committees are themselves doctors, and the medical profession naturally owes them a particular debt.

* * *

The need for this form of voluntary service, however, raises the question, whether we may not be in danger of overstraining our resources. After all, there are many other forms of important voluntary service, and the number of people who are sufficiently interested, and can spare the time for such work, is necessarily limited. The other day I made a rough calculation of the number of man-hours required to be voluntarily contributed in order to run a regional hospital board for a year. I was astonished at the result; and if one takes into account the very much larger number of hospital management committees, each making its own substantial demand upon their time in man- and woman-hours, the total is very great indeed. Here we meet with a problem rather like that of London traffic. The bigger the city and the greater the volume of work done in it, the greater the number of cars needed, and the more cars, the more difficult it becomes to get about to do the work. And just as the congestion of London traffic threatens to make movement impossible, so the congestion of business created both for lay and medical committees by the Health Service tends to absorb more time than either can afford to give, in the case of doctors to interfere either with their work or with their hard-earned and all too brief leisure, and indeed to bring business to a standstill. Permanent Session, by Democracy out of State Service, is not a fast-moving horse. I do not know the complete answer. It is certainly not more officials, and it cannot indefinitely be more committees, not even another committee to consider this problem! For if it is to be solved it must be solved in part at least by the committees themselves.

Perhaps the key to the situation is to be found in the relations between the chairman of the committee and the chief administrator. Mutual confidence, flexibility, and a willingness on the part of each to give and take responsibility, and be judged by the results, will save many committee man-hours a year, with no loss of efficiency or good relations.

And good relations are essential if this great social adventure of the National Health Service is to work, not merely smoothly, but also efficiently. G. K. Chesterton once wrote a book which he called *What is Wrong with the World?* and in the introduction he described humorously the embarrassment which the title caused him while he was writing it, because, when visitors to the house inquired after him, his wife would reply: "Oh, my husband is in his study, doing *What is Wrong.*" Some people seem to feel much the same about the Health Service, especially about its administrators. If you want to know where they are, they are in their bureaucratic offices, doing what is wrong. Of course, we must be vigilant to detect abuses, and to get them put right, but excessive criticism is harmful, and emotion is a bad counsellor, especially when it produces sweeping generalisations. Let us give our administrative colleagues, many of whom are themselves doctors, the credit for at least as much understanding and commonsense as we claim for ourselves. But, while I do not believe that the exaggerated statements which have been made are justified, I think they spring from a genuine apprehension about the future, and that there is a real anxiety about a matter which is important for the welfare both of the medical profession and of the Health Service.

* * *

The Health Service has been in existence now for only seven years. During that time a very large amount of work has been done, much of it by officials of the Ministry of Health and the consultants in close collaboration, to overcome the difficulties inevitable in the transitional period of what is, in one of its aspects, a social revolution. Considering the magnitude of the change, I believe the difficulties have been overcome with remarkable success. Admittedly, not all problems have been solved, because in the complicated conditions with which we have had to deal it has often been impossible to foresee the full consequences of the measures taken. One result has been that some doctors have suffered hardship. Neither side has always been right, and sometimes we have both been wrong. Nevertheless, I believe that the large measure of success which has been achieved has been due to a determination on the part of all concerned, and not least the officials of the Ministry of Health, to preserve what was good in the old order of things, while welcoming the benefits which have come from the new organisation.

One of the values which we have striven to preserve is the independent professional status of the doctor. It has been done successfully so far, and I believe that we shall succeed in firmly establishing this fundamental principle as part of the new order. But, among the many people, who through regional boards and hospital management committees are brought for the first time into close contact with the management of hospitals and the work of doctors, there may be some who do not understand the principle, and therefore do not see the necessity for maintaining it.

Let me, therefore, try to explain what it is. The crux of the matter is that the relationship between doctor and patient derives from the doctor's profession, and involves duties and responsibilities which are completely unrelated to the source of his remuneration. It makes no difference to the doctor's professional obligations to his patient whether he is paid by the patient, or by the State, or for that matter is not paid at all. In addition to this primary obligation to the patient, he has, of course, if he is paid by the State, to do the work, for which he is paid, faithfully; and this is an obligation which he shares with everyone who receives a salary, whether from the State or from any other source. I believe that a very great majority of doctors do their

* An address delivered at the annual meeting of the Enfield Group Hospital Management Committee.

work for the Health Service faithfully, and indeed many do far more than they are, or can be, paid for. The doctor's position in the Health Service creates difficulties only when there is confusion between his two obligations. The doctor's obligation to the patient, however, is in its own sphere absolute, and entirely beyond the scope of the employing authority, which, therefore, has no right to dictate to the individual doctor on any matter of professional practice or ethics. The most it can do, if it feels concerned in such matters, is to refer them to its appropriate medical advisory committee.

Now, if I am right, doctors occupy, and will continue to occupy, a unique position in the Health Service. Others who work in the service also have their own professional obligations, but the doctor alone has the added responsibility of caring for the patient as a whole, and directing the work of others, who render the patient service.

His professional independence within the Health Service is not merely an exaggerated form of sectionalism: it is essential to the welfare of the Health Service, and indirectly to the welfare of society. I do not believe that anyone would wish to be treated in hospital by a doctor who had some other professional allegiance than one solely directed to his patient's welfare. Those of us who have to spend much time considering and discussing general principles, admittedly of great importance, have to be careful to preserve our sense of proportion, and not to regard isolated cases as representative of what is going on generally. That is why I find it so refreshing and stimulating to meet, as I have the opportunity of doing today, the laymen and doctors who are getting on with the job. I believe that in general the doctor's professional responsibility *is* recognised and respected. It gives rise to no difficulties, and hospital authorities and doctors are working harmoniously together.

* * *

We are fond of boasting that we are not a logical nation. Though we are often somewhat vague about theoretical principles, we have a habit of doing the right thing intuitively in practice, and then discovering afterwards that we have done it on principle. So far we have done it successfully in launching the Health Service; and I have every hope, and see every prospect, that, if laymen and doctors go forward together in the same spirit of goodwill and mutual understanding, we shall succeed in creating a service which will be a model for the whole world.

International Congresses

VITAMIN E

THE 3rd International Congress on vitamin E, which followed those of 1939 in London and of 1949 in New York, was held in Venice on Sept. 5–8, under the presidency of Prof. Carlo Foa. About 160 members from 16 nations attended. The communications included both reviews by invited lecturers on reports in specified fields of research, and reports of original work in these fields. The proceedings were greatly helped by the simultaneous translation of the communications, through headphones, into three other languages.

The heavy accumulation of papers on vitamin E, assessed by P. L. Harris at about 1600, justified the calling of the conference but made heavy work for the lecturers. In experimental studies on the effect of the vitamin on metabolism much interest has centred on the effect of unsaturated fats in aggravating the symptoms of deficiency, on the breakdown products of the vitamin in the body, and on the extent to which the vitamin can be replaced in its functions by certain "redox" substances, including methylene-blue. H. Dam's description of vitamin E as an "in-vivo antioxidant" continues in favour. Opinions are divided, however, as to whether this action is exerted evenly throughout the body, or is concentrated on special sites, such as the pituitary, adrenals, and thyroid. The discovery by J. Green, and other British workers, that cereal products contain two new forms of tocopherol (named ε and ξ) has raised interest as to their biological activity and practical importance in our diet. With the previously known modifications (α, β, γ, and δ) the total number of tocopherols is now six.

In contrast to our detailed knowledge of the importance of vitamin E for laboratory animals, great uncertainty remains as to its value in the treatment of disease in man. At the 2nd congress sanguine hopes were raised by Dr. Evan Shute that vitamin E might revolutionise the treatment of diseases of the heart and peripheral vascular system. At the present congress he displayed further impressive photographic records showing the favourable progress of various peripheral vascular injuries, caused by accident, burns, or infection, after treatment with tocopherol. As on previous occasions sceptics might ascribe most of the cures to spontaneous recovery under the influence of adequate hospital treatment. In Shute's opinion, however, the effect of tocopherol is so striking that demands for comparisons with controls untreated with vitamin E seem inhuman. V. R. O'Connor would presumably support this view in regard to cardiac and renal patients; and in the veterinary field N. H. Lambert is enthusiastic on the effect of tocopherol in warding off the effects of old age in dogs. Convincing statistical evidence seems essential before tocopherol therapy can be accepted as more than an expensive placebo. An investigation by Maurice Lee on the progress of leg ulcers, with or without tocopherol, is therefore welcome. The vitamin appeared to accelerate healing slightly; the difference was statistically significant in patients with a history of deep venous thrombosis. A point on which all other workers agree is that the doses given by Shute and his followers are greatly in excess of the normal requirements of the body. The alleged action of the vitamin cannot therefore be due to the correction of dietary deficiency.

The prominence of muscular dystrophy as an effect of experimental avitaminosis E suggested the use of tocopherol in the treatment of muscular dystrophy in man. The results so far obtained have been very disappointing. Even in instances where tocopherol has influenced the muscle biochemically, as evidenced by decreased creatine excretion, the progress of the disease has been unaffected. An ingenious "split-frame" film by K. E. Mason, showing side by side motion pictures of dystrophic children photographed after various periods of treatment, reinforced this sad conclusion. In contrast K. L. Blaxter and others have reported that many forms of muscular dystrophy in farm animals respond readily to treatment with tocopherol.

Several workers mentioned the novel finding that tocopherol can influence the clotting-time of blood. In-vitro clotting appears to be slightly accelerated, which is perhaps difficult to reconcile with the supposed favourable effect of the vitamin in the treatment of thrombosis. E. Raverdino considers that tocopherol may be helpful, in combination with anticoagulants, in treating certain vascular abnormalities of the retina. P. Prosperi and A. Lottini observed beneficial effects in the treatment of a case of hæmophilia.

A pleasing feature of the congress was the evidence of intensive and fertile research on vitamin E in Italy. As the fruit of both clear scientific insight and high technical skill a communication by Prof. M. Aloisi, dealing with the microscopic changes in muscle made dystrophic by vitamin-E deficiency, earned the admiration of all present.

The Wider World

FORMOSA

The Beautiful Island

FROM A CORRESPONDENT

BEFORE the war few of us knew much of Formosa—though we may have remembered that Manson spent some time at Kaohsiung as port medical officer before he went to Amoy. But during the past year the name has appeared at uncomfortably short intervals in the newspapers. Actually this name of Ilha Formosa, given it by the Portuguese, has been changed by Nationalist sentiment, and the island has been renamed Taiwan—the terraced bay. Indeed, it is both terraced and beautiful.

Taiwan lies 100 miles off the Fukien coast. Geographically, and strategically, it is part of the chain of mountainous islands that include Korea, Japan, Okinawa, and the Philippines, and it shares their typhoons and earthquakes, though it is twenty years since the last disastrous earthquake. From north to south run a series of mountain chains with peaks rising to 14,000 ft., so that roads from east to west exist only at each end of the island. On the east side the mountains run close to the sea leaving only small plains of intensively cultivated rice, and in some places the sea-cliffs drop 3000 ft. sheer to the Pacific. On the west there is a plain 10–30 miles wide, that is the heart of the country. It is laid out in terraced paddy-fields, irrigated by the rivers from the mountains, and patrolled by egrets, and it grows two crops of rice a year, and in the south three. Sugar and sweet potatoes are other main crops; vegetables, bananas, pineapple, squashes, anything will grow in this carefully watered land except Irish potatoes, soy-bean, and apple. Ducks, hog-raising, sea and river fishing provide marginal amounts of animal protein. As you climb the mountains the terraces of rice grow smaller and smaller and give way to kassava, till this too is replaced by the tea-gardens. The mountains go on up in forests of camphor and oak, tree fern, and accacia, so wastefully cut in the past that it is difficult now to get out the mature timber, and afforestation is only slowly catching up erosion. The flowering shrubs and trees decorate the plain and the accessible parts of the forest—azalea, oleander, hibiscus, phœnix trees, and flame-of-the-forest, orchids, poinsinetta, and a dozen others whose Chinese names I cannot remember. Industries are springing up, and coal and aluminium are local products. The farmer is not rich, but now that the large holdings have been split up he is better off than ever before. The average farm is under 3 acres and the only machine employed is the pedal-operated threshing-machine.

The weather varies in relation to the mountains. In the north and east there is rain all round the year, making Keelung one of the wettest ports in the world. Yet fifty miles south of Taipei it rains only in June, July, and August, and the winter is warm and rainless. Taiwan has been peopled over the last 500 years by successive waves of migration from the mainland, driving the aborigine inhabitants back into the mountains. Of the 10 million people, $7^1/_2$ million came from Fukien and speak Taiwanese (Amoy). About 1 million came from the region of Canton, whose inhabitants are great travellers, and speak Hakanese. The 200,000 aborigines speak several dialects of non-Chinese origin.

HISTORICAL BACKGROUND

Before the Japanese came in 1895 the population was about 3 million, ravaged by misgovernment as a Chinese province, and by epidemic disease, drought, and starvation. The Japanese created a most successful colony with the development of irrigation, hydro-electric schemes, modern methods of communication, and simple public-health measures, so that the population doubled between 1905 and 1940. Japanese was used as a lingua-franca and was the language used in the schools. This colonial government was not utopian, for the Japanese were there to make money out of Taiwan and they succeeded; but the Taiwanese reaped great benefits, including the most complete registration system in the world. During these years the death-rate fell from 33 to 18, and the infant-mortality rate from 180 to 120, while the birth-rate remained, and remains, in the 40s. Incidentally the present death-rate is officially 8 and the infant-mortality rate 30, though the latter figure is in fact probably higher.

The end of the late war brought an outbreak of jingoism that destroyed much that was good; but perhaps this was inevitable after fifty years of an oppression that was sometimes brutal. The first Chinese government produced a wave of strikes and civil disturbance. Several thousand Taiwanese were killed and the governor was brought to trial for the part he had played and was publicly executed. Since then reforms and progress have gone forward steadily. The Communist successes on the mainland brought a growing flood of refugees to Taiwan, and in 1949 the Chinese government arrived in Taipei, the capital. The years that followed have been uneasy ones, with a national government sitting on top of the provincial government and dreaming of the 17th century when Chen Chung-Kun captured Taiwan from the Dutch and used it as a base for his unsuccessful attempt to drive the Manchus out of China.

THE PEOPLE AND THEIR HEALTH

The Taiwanese are most likeable, courteous, and humorous. Education is compulsory and most children go to school at some time or other, but schools are crowded and many slip through the net of compulsory attendance, and stay at home to give a hand there. The Taiwanese are better off than the people in most Asian countries. Bicycles seem almost as common as in Denmark, beggars are rare, and the starvation that is round the corner of the street in much of Asia does not exist here. There is little wealth and what there is is not displayed, for austerity is the fashion. There are not many private cars, but the number grows as the Americans who have served their term on the island sell their cars. It is just as well that there are still so few, because the Taiwanese—men, women, and children—are still attuned to the speed of the buffalo and bullock and cheerfully disregard the lethal potentiality of the automobile.

Fig. 1—Aborigine village.

There are about 4000 doctors in practice and 2000 nurses. Under the Japanese, medicine was almost the only profession open to the bright young man. The teaching was rigid and authoritarian and the litigious customs of the country made it difficult for him to adopt many of the modern methods of treatment.

The medical school of the National (formerly Imperial) University is now largely staffed by men who have spent some time in the United States, and better standards of work are spreading through the island. Some 365 health stations, each serving a population of about 30,000, have been built, nearly all since the war. These are neat, simple, one-storey, concrete buildings with a staff of 1 or 2 doctors, 2 to 4 nurses, a sanitary inspector, and a clerk. In the mornings clinics are held for patients who cannot afford, or do not choose, private doctors. Patients are assessed at how much they can afford to pay, but treatment and drugs can be given free of charge. The afternoons are spent in public-health work, including clinics for maternity and child welfare, school health, immunisation, and the treatment of trachoma. Post-graduate training in preventive medicine, organised by the provincial health administration with the help of the World Health Organisation, UNICEF, and other bodies, is improving the amount and quality of the work done. Till now, except at the University Hospital in Taipei, the work of the hospitals has been below that of the health stations. In view of the economic problems of the country it is perhaps as well that for the present the greatest effort should be concentrated on preventive medicine and medical education.

Fig. 2—The younger of these two sisters shows the hair-changes of protein-deficiency not amounting to kwashiorkor.

Malaria has practically disappeared since the W.H.O. team first began to show how D.D.T. could be used. Despite what American and British textbooks say, schistosomiasis does not exist. If only we knew why it did not exist here, whereas it does in all the neighbouring countries, we might be able to control its transmission. Tuberculosis and syphilis are common, leprosy unusual. Ankylostomiasis and amœbiasis are common, ascariasis universal. Poliomyelitis, until recently unrecognised, is now beginning to occur in small localised epidemics in children under 5, just as it has in most tropical islands since the war. When I first came to Taiwan I did not expect to find much delinquency and psychoneuroses, but the familiar Occidental pattern of psychosomatic disorders and mental ill health seem to be in evidence. Ariboflavinosis and vitamin-A deficiencies are common in school-children, and the child of 10–18 months often gets too little protein for his needs (fig. 2). How the coolie and the farm-labourer do their work and maintain their weight and strength is a mystery to me. As elsewhere, the women vary in beauty, but both men and women have beautifully modelled legs. The townsman is slight and narrow-chested, but the farmer and the manual worker have fine, strong bodies. Children are made much of and are always welcome; they behave much as children do elsewhere but schools are pretty restrictive and remind me of the classrooms of another educational era.

The Taiwanese are not a martial race, and they dislike the idea of being involved in a civil war which still appears to be someone else's problem, though it has been said that the one thing they might fight for would be to help the mainlanders back to the mainland.

Politics apart, the years to come will have problems enough in store, for rising numbers on so densely populated an island may soon produce violent economic changes. But the Taiwanese can accept an impossible situation cheerfully, and meantime he takes the greatest pleasure in sharing with you the good things of Formosa—good food, good company, and a wonderful countryside.

Before Our Time

BRITISH DOCTORS AT PADUA UNIVERSITY*

ANDRA BOSATRA
M.D. Padua

EVEN before the foundation of its university in 1222, Padua was recognised as a centre of international culture; and between the 13th and 18th centuries it attracted students from many countries, including some distinguished British doctors.

According to ancient customs, many of which still persist in some British and American universities, the students elected each year a rector, who was given great authority and prestige, not only over them, but also with the civil and religious authority of the city. At first there was only one rector but later the students were grouped into "nations," each of which elected a rector of its own. These nations became the basic unit of university administration. A document of 1228 mentions the English as belonging, with the French and Normans to the nation of *Langue d'oeil*. Later they joined the "German" nation which included Flemings, Scandinavians, and Poles. The number of English students apparently increased rapidly, and in 1331 they formed, with the Scots, a nation of their own. The Scots, however, liked to be kept distinct from the English, to such a point that in 1534 they joined with another nation, and did not re-join the English till 1602.

In 1399 the faculties of arts, medicine, and natural philosophy were separated from the older faculty of law and given autonomous status. Anatomical research was authorised by the religious and civil authorities; and Alexander Benedetti, a professor of the university, discussed in a treatise the problem of the construction of an anatomy theatre. These developments drew more British students and doctors to Padua. The first important group of which we have news arrived from Oxford in the second half of the 15th century, led by John Tiptoft, Earl of Worcester, and it included students of law and medicine. Though many of these remained for some years, for others Padua was only a station of their *peregrinatio academica*.

Among these student visitors the first important medical figure we meet is *John Chambers*. A priest and a master of arts of Oxford, he came to Padua in the last years of the 15th century to study medicine. After he returned to England, he became personal physician to Henry VIII. He collaborated with Linacre in founding the Royal College of Physicians of London and, as counsellor of the king, he shared in the medical organisation of England. At the end of his life Chambers was warden of Merton College, Oxford.

* Based on an address given during the visit to Padua last year of the Visiting Association of Throat and Ear Surgeons of Great Britain.

Thomas Linacre himself came to Italy in 1488, with William of Selling whose pupil he had been at Oxford. After visiting Florence, he moved to Padua to study medicine, and took his degree in 1492. Besides the anatomist Benedetti, his masters at Padua included Nicolò Leoniceno, a famous Greek scholar; and he was also a friend of the great editor, Aldo Manuzio. When he returned to England he lectured at Oxford and Cambridge; he became a personal physician to Henry VIII; and he was also tutor to Princess Mary. Yet he still found time to edit the first English translations of Galen.

Somewhere about the year 1540 another student of medicine who has achieved fame came to Padua—*John Caius*. He was the faithful pupil of Giovan Battista da Monte, who was the first teacher to bring students into the hospital wards, so as to talk to the patients and to study their illnesses. Caius, in proof of his devotion and esteem for his master, quoted him immediately after Galen in the titles of his books.

Thomas Phayer, also came to Padua, but it is not known whether he studied medicine or law, but he later practised both professions. He was the author of the first English treatise on pædiatrics and of the first translation of Virgil's *Aeneid*.

Between 1521 and 1525, as part of his peregrination, *John Clement* visited Padua. He, too, was a physician to Henry VIII, he translated Greek classics, and he married the daughter of Sir Thomas More. *Edward Jorden*, who took his medical degree at Padua towards the end of the 16th century, was the author of the first English psychiatric study, which includes the case-history of a woman with laryngeal spasm of hysterical origin.

And now, at the end of this glorious century, we meet *William Harvey*, who came to Padua to study under Fabricius d'Acquapendente, in the new anatomy theatre, the first in the world, which had been built in 1595. Near by, from a roughly made professorial chair, erected in the open to satisfy the numerous students, Galileo Galilei demonstrated his universal laws. Harvey received his degree on April 25, 1602, from the hands of a Palatine count, Sigismondo Capodolista; for he was not a Catholic and the Venetian Republic had obtained leave that non-catholic students should receive their degrees from some Paduan counts of imperial title rather than from the bishop.

Fabricius, who had deeply studied the venous system, had probably a big influence on Harvey's work on the circulation. Moreover, both the idea of the circulation, and the term itself, were known before this work was done. But Harvey's achievement was to demonstrate the phenomenon, both qualitatively and quantitatively, so that his inquiry into the circulation of the blood can be regarded as the first really modern work in experimental physiology. In his method we can properly recognise Galileo's teaching; for Galileo was the father of experimental research and exercised a profound influence also in medicine, which he had studied as a young man.

* * *

Those I have named here are only the most eminent figures of this period. How numerous were their less famous colleagues is shown by the fact that the roll of the Royal College of Physicians between 1502 and 1671 includes at least 57 men who had taken their degrees at Padua. To these we must add the greater number of students who frequented this university for a brief time; and equally we must take note of the continuous exchange of news and ideas so fervid among the scholars of that epoch—a reciprocal influence evident, for example, in the support which Ramazzini, of this university, gave to Sydenham's theories of the *genius epidemicus*. Our meeting today prolongs the community of spirit and culture which is the solid basis of friendship between our countries.

Public Health

"Random Reflections"

"I thought it might be useful to try to convey something of my own faith in the value of our work and my confidence in our future," said Dr. Charles White in his presidential address to the Society of Medical Officers of Health on Sept. 22. It is, he thinks, no good complaining that the curative services attract most attention: "of course they do and will continue to do so." He hoped that those engaged in the treatment of disease would become more generous in their acknowledgement of public-health work and more anxious to coöperate in it. For their part, those engaged in public health should be generous in acknowledging the achievements of curative medicine but should at the same time have faith in themselves, in the value of what they have done, and in the possibility of doing even greater things.

Medical officers of health had been heard to complain that the National Health Service Act had left them only environmental hygiene and epidemiology; but such a complaint, he felt, implied too narrow a view of the meaning of these words:

"Environmental hygiene in its restricted sense has been limited to the hygiene of man's physical surroundings. It is a branch of public-health work which I think some medical officers of health have in recent years tended to hand over to non-medical staff or to other departments of the local authority, but I agree with Sir William Savage that medical officers should retain a close interest and association with it. In the first place their medical training and experience has developed their powers of observation and their capacity to weigh the relative importance of the conditions they observe. They expect to have to use their discretion in prescribing treatment and not to be bound by hard and fast rules and standards which are so beloved by the lay staff. In the second place it has been my experience that sanitary inspectors welcome the interest of the medical officer of health in their work and the opportunity of discussing their problems with him. They realise that the M.O.H. cannot be as familiar as they are with all the detail of the practical work in which they are engaged day by day, but they know that he understands the underlying principles and can bring a trained mind to the consideration of such principles in particular cases. I think sanitary inspectors generally are quite happy to be members of a team of which the M.O.H. is captain, but if the M.O.H. does not play then they not unnaturally want to be independent."

But environmental hygiene meant much more than the physical surroundings which affect health; it included the personal and social relationships which can have a profound effect on the individual, and thus not only on his mental but on his physical health. As regards mental ill health, there was scope for much more preventive work at all ages, which in his opinion could be developed only by the public-health service, in coöperation with general practitioners and certain voluntary organisations.

The tendency had been to regard epidemiology as the study only of communicable diseases; but Dr. White thought the M.O.H. should accept J. N. Morris's broader definition of epidemiology as "the study of health and disease of populations in relation to their environment and ways of living."

In discussing the advances that the M.O.H. might make into new territory with the aid of allies, Dr. White numbered among those allies the voluntary societies. In one respect these had a great advantage over official bodies: they could take action in individual cases, so far as their funds permit, without committing themselves to similar action in all the similar cases that might present themselves; and this made it easier for them to do pioneer work on a small scale. Many people were still anxious to give personal service to those in misfortune or distress, but on the other hand it was nowadays far harder to collect money for charitable purposes. "While

obviously no voluntary organisation can be given a free hand to spend public money, I suggest that it would be well worth while widening the range of activities in which voluntary societies may be subsidised by local authorities."

Touching in conclusion on the future of local government, "politically almost too hot to touch," he remarked:

"From the point of view of the M.O.H. I think the unit of local government should be the smallest that is capable of financing efficient public-health services. Too large a unit is remote and impersonal; too small a unit cannot afford to do its job properly. Moreover, I feel sure that if the ambitious young medical graduate is to be attracted to the public-health service, he must feel that he has a reasonable chance of obtaining ultimately an independent command as a medical officer of health. The independent commands are too few in number at the present time."

Dr. White holds the presidency in the centenary year of the society. Sir John Simon, the first president, was, like him, medical officer of health for the City of London.

Poliomyelitis

Speaking at the annual meeting of the Infantile Paralysis Fellowship, held in Edinburgh on Sept. 24, Dr. Dennis Geffen, medical officer of health for St. Pancras and Hampstead, remarked that there was now conclusive evidence that the poliomyelitis virus grew in the intestine and was excreted in the fæces, and that the spread was alimentary rather than, or as well as, respiratory. Of prevention Dr. Geffen said: "it is obvious that a person suffering from the disease should be isolated and that all methods of antisepsis and disinfection should be adopted to prevent the spread of the virus. Contacts too must be isolated, and the recommended period is at present three weeks. This isolation must apply particularly to persons who are associated with children or who come in contact with food. I admit this is a counsel of perfection and sometimes very difficult to follow in practice. On the other hand the first case of poliomyelitis in a district should be treated as highly infectious, for I believe that by isolation of the patient and contacts you may prevent the spread of the disease in epidemic form."

Dr. Geffen went on to declare that poliomyelitis was a mild disease, with the exception of one complication.

"This complication is the invasion of the nervous system, the destruction of nerve-cells, and the production of paralysis. . . . There seems to be some sort of barrier between the nervous system and the rest of the body which normally is sufficient to prevent the passage of the virus of poliomyelitis. Under certain circumstances this barrier is weakened and breaks down. It may be that local injury, over-fatigue, operations, injections, and the like may cause this barrier to break down locally. It is known to us that certain drugs weaken this barrier. There is, may I say, at least a hope that in due course we may find other drugs that strengthen it. It is possible that the barrier is weaker in males than in females. It is weaker in youth than in old age. It is believed to be weaker in pregnancy than at other times, and it is thought that pregnant women are very susceptible to paralytic poliomyelitis."

After reviewing experience with the Salk vaccine Dr. Geffen said that we needed to be satisfied that this was effective, was safe, and would produce lasting immunity.

NOTIFICATIONS IN ENGLAND AND WALES

In the week ended Sept. 17 (37th week) uncorrected notifications of poliomyelitis in England and Wales were as follows (figures for the previous week in parentheses): paralytic 193 (206), non-paralytic 218 (252); total 411 (458). Regionally notifications in the 37th week, compared with those in the 36th week, decreased in the London and South-Eastern region, and in the North-Western, North Midland, and Southern regions. There were rises in the Northern, Eastern, South-Western, and Midland regions and in Wales. The excess of non-paralytic over paralytic cases in the 37th week was due largely to notifications from Middlesex, especially Willesden, and from Surrey.

Total uncorrected notifications in the 37th week of each of the years since 1950 (proportion of paralytic cases in parentheses) were as follows: 1950, 479 (60·9%); 1951, 90 (46·9%); 1952, 184 (62·5%); 1953, 227 (54·2%); 1954, 92 (63·0%); 1955, 411 (24·9%).

Hitherto this year the incidence for England and Wales as a whole has been 8·7 per 100,000.

Milk-borne Tuberculosis

Not so long ago tuberculosis of bovine origin was a common disease in this country, but Dr. Lethem of the Ministry of Health now feels able to say[1] that it has "followed cholera and plague into the limbo of the past." The results of thirty years' preventive work are reflected in the Registrar-General's figures for abdominal tuberculosis in 1921 and in 1953 in children under five years of age. The most significant change is in London, where the deaths per million of children dropped from 136 in 1921 to 4 in 1953. Lethem attributes this great improvement to the fact that nearly all London's milk today is pasteurised or sterilised, whereas in 1921 only about half was heat-treated. The deaths for rural districts also fell considerably, from 252 per million of children in 1921 to 12 in 1953, but untreated and untested milk is still being consumed in unknown amounts in country districts. In broad terms Lethem can correctly claim that "the all too common ailment of childhood, 'glands in the neck,' once an accepted feature of English life, has disappeared." But Dr. C. D. L. Lycett's account of tuberculous adenitis in the Marlborough area last year,[2] with at least 15 cases traced to one cow, shows what can still happen.

In proclaiming the good news that "the long drawn out battle for safe milk—or at least for tubercle free milk—has been virtually won," Lethem says that the proportion of milk produced from attested (tuberculosis-free) herds is now 58%. Tuberculosis has lately been cleared from four more areas (one in North-West England, one in mid-Wales, and two in Scotland) which were declared eradication areas by the Departments of Agriculture last March. Since then compulsory tuberculosis-testing has been carried out in the 385 herds in these areas not previously attested; reactors have been removed and slaughtered; and from Oct. 1 the four eradication areas have become attested areas. Approximately a fifth of all herds in Great Britain are now in such areas. The Ministry of Agriculture says that there were about 5·3 million cattle in attested herds by June this year, compared with 2·25 millions in October, 1950, and adds that "at the present rate of progress it is hoped that the country will be free of bovine tuberculosis in about the next ten years."

Medicine and the Law

Capital Punishment in New Zealand

In our leader on the death penalty[3] we included New Zealand among the countries where capital punishment had been abolished between 1870 and 1942. A correspondent has drawn our attention to the fact that the death penalty was reintroduced in New Zealand in 1950, nine years after its abolition in 1941. In view of this change of procedure the numbers of convictions for murder over these years are of interest:

For the 9 years before abolition: 10.
For the 9 years during abolition: 31.
For the 4½ years since reintroduction: 17.

These figures offer no clear support for either the abolition or the retention of the death penalty and their significance is further obscured because from 1935 to 1941, though the death penalty was legally still in force, in practice all death sentences were commuted to imprisonment for life.

1. Lethem, W. A. *Mon. Bull. Minist. Hlth Lab. Serv.* September, 1955, p. 144.
2. Annual report of the Medical Officer of Health for Wiltshire County Council. 1954.
3. *Lancet*, July 23, 1955, p. 181.

In England Now

A Running Commentary by Peripatetic Correspondents

ALL this chat that is going on about the identification of human intersexes by skin biopsy and examination of the polymorphs prompts us to publicise the case of our budgerigar. Two years ago the thought came to us that the long winter evenings of our declining years might be enlivened if we had a budgerigar to recite to us. When we get tired of Pop Goes the Weasel, we thought, we will switch him on to Mary had a Little Lamb, and when the sentiments of Rockabye Baby have begun to cloy we will teach him Pat-a-cake, Pat-a-cake, Baker's Man. Right, then, we said, we shall buy a budgerigar.

When we brought him home he was surrounded by quantities of budgerigar seed, a supply of golden budgerigar sand, a small sack of budgerigar grit, and a packet of budgerigar cuttlefish bone (packed on the sun-drenched uplands and full of budgerigar vitamins). Also we had a small budgerigar booklet. "Male birds," said the budgerigar booklet on p. 1, "can be identified by the blue colour of the mask at the base of the beak (see illust., Fig. 1)." We looked at Billy (he had been christened in the car). Sure enough his mask was a pale blue and entirely consonant with the appearances as shown in illust., Fig. 1. Having satisfied ourselves that the new member of the household was indeed a male, and therefore a born entertainer, we expended some thousands of invaluable man-hours, to say nothing of woman-hours and child-hours, in trying to get his name through our budgerigar's ivory skull. "Billy!" we would begin patiently over the breakfast table in a level calm voice designed to inspire confidence. "Billy!!" we cried jocularly over lunch: "Billy!" we croaked hoarsely at supper. "Billy!!!" we roared at bedtime when our control had begun to crack.

After six months of nervous and laryngeal exhaustion, during which our budgerigar consumed several pounds of budgerigar seed, a mountain of budgerigar grit, and a small fortune in sun-drenched cuttlefish bones, we observed that his mask was changing colour to a medium brown. A horrible suspicion seized us, and we dived at once into our budgerigar booklet. Yes, our suspicions were well founded. Billy's mask no longer corresponded to illust., Fig. 1, but was in all respects identical with illust., Fig. 2. The matter was clinched the other day when he won second prize as a female in the Miscellaneous Class of our local R.S.P.C.A. show. (First was a guineapig we know well, from down the road.)

Our concept of our budgerigar as an accomplished diseur (or even diseuse) has been abandoned, and we are reconciled to spending our declining years in the company of a series of deafening feminine steam-whistle cheeps. But we must confess we find the whole thing rather disturbing. We think perhaps it must have been that nasty thermonuclear stuff that did it.

* * *

So Smedley's Hydro at Matlock closed last week. It seems a pity, after an existence of more than a hundred years, although no-one today would deny that the place has outlived its original purpose.

John Smedley, who started it, was certainly a queer card. His business was that of a hosiery manufacturer at the village of Lea a mile or two from Matlock, but his hobbies were evangelical preaching and the practice of hydropathy; indeed at his mill he conducted his own brand of religious service, even going to the length of compiling a special prayer-book for the purpose. But he concerned himself with the bodies as well as the souls of his workpeople, and quarters were fitted up at the factory where they were obliged to submit themselves to the water cure, which had been made popular in the early years of the 19th century at Gräfenberg, by Vincenz Priessnitz, who, like Smedley, was without medical qualification. As with other cults before and since, this unorthodox therapy had a vogue for a time, and treatment was much sought after at Smedley's factory. At length a counterpart of the institution at Gräfenberg was built on Matlock Bank for the accommodation of the people who wished to undergo hydropathic treatment, and this was the beginning of the famous hydro—the first of its kind in Britain. Extensive additions and alterations took place rapidly, and long before the end of the century the building was substantially as it stands today.

The arrangements for treatment at the hosiery factory were eventually discontinued, and after Smedley's death a small memorial hospital was opened near the hydro itself to enable the less well-to-do people to enjoy the benefits of the cure. That hospital was taken over by the Sheffield Regional Hospital Board in 1948, but it is no longer used specifically to provide hydropathic treatment. A patient I saw the other day had had a stay there after a radical cure for hernia elsewhere; he referred to it as Smedley's *Hydraulic* Institution. Sic transit gloria!

* * *

Nature notes.—Our summer migrants are now home again, in their bronzy autumn plumage. The guns are out and soon reports will be heard from coppice and hanger, among them the quaint call-note—now silent for months—which we can best render as "Gillỹ bo! Gillỹ bo!" Sleek specimens of *Pract. familiensis*, in the South often called geepees, may be marked scuttling about the hedgerows to replenish their store of berries—known locally as dank worts—'gainst winter snows. Though the ditches are still gay with bachelor's-buttons, the return of the butlerbird from Anatolia heralds frosty weather and frozen pools. In the sky, macleods gather and depart.

Garden reminders—Collect leaves in heaps for the publisher. File cuttings.

* * *

Merlin's Corner

The pendant chain works like a charm. The first time I tried it my youngest son felt perfectly well again in a yard or two. A friend's Welsh sheepdog begins to salivate and eventually vomits if the chain is not down. But when the chain is down the dog neither salivates nor vomits. Though the chain works like a charm, I am satisfied that it is not a charm. But can anyone say exactly how it does work?

The dangling chain is pure magic. The count among those who have tried it is one for and five against. Scientifically, of course, it is all nonsense because modern tyres permit a small leak of static electricity to the ground all the time. But "fast" touring in a veteran car on a dry day can produce some interesting phenomena as a passenger places foot to ground—particularly if he has a handlebar moustache.

I can confirm that a chain suspended from the back-axle prevents car-sickness. It is, in my experience, particularly effective with dogs. Since we adopted this method a year ago our dog has been sick in the car only once. Investigation showed that the chain had become tangled up in the under parts of the chassis; after it had been released there was no recurrence. The technique has one undesirable side-effect. Well-meaning fellow-motorists will wave you to a standstill to point out that a component has become semi-detached.

Of course the pendant chain works; and there's no magic about it. Last year someone told me that car-sickness could be prevented in this way; but I forgot about this and we set out from London for the North of Scotland unprepared. My 14-year-old daughter, car-sick as ever, had a troubled journey. Coming south again, she hung her head out of the window like a keen spaniel sniffing the air; but it was no use. During one of our repeated stops I remembered about the chain. On an old wall I found a broken strand of wire which I fixed to the rear bumper so that it trailed on the ground. I told no-one of this. The next two hours' travelling was accomplished in unaccustomed tranquillity, and my daughter, who had been unable to face lunch, ate a good tea. Furtively I detached the wire; and the girl, pale and nauseated, touched no further food that day. She had been puzzled by her afternoon's freedom from misery, and was not at all gratified at having been the subject of a controlled trial. How does it work? Surely it is by earthing of static electricity. With the chain down I no longer have tingling in the fingers at the end of a long journey.

* * *

From our Advertisement Columns.—"Boyle's machine (D model) in good condition. £20 or exchange good D.B. hammerless shotgun." A return to blunderbuss methods of anæsthesia?

Letters to the Editor

PROFESSIONAL RESPONSIBILITY

SIR,—Sir Russell Brain in his letter last week writes that neither the Minister nor any regional or hospital authority has the *moral* right to interfere in the exercise of a doctor's professional duty to his patient which is "to treat him to the best of his own judgment—subject only, if he holds a subordinate post, to the direction of his professional chief—and to observe the standards of professional ethics." We can all agree with this wholeheartedly. However, the plain fact is that these authorities do most certainly have the *legal* right to do just that as a result of the various judgments in England and in Scotland which, interpreting the situation created by the National Health Service Acts, have established the master and servant relationship between hospital authorities and the doctors on their staffs. The action of the hospital management committee quoted by Dr. Sherwood (Sept. 17) is an excellent example of the kind of professional interference and direction which, however offensive morally to Sir Russell and the rest of us, hospital authorities will find it desirable to exercise to protect from litigation the public funds with which they have been entrusted.

Sir Russell, attempting, in my view without much relevance, to draw a distinction between a doctor's professional duty to his patient and his obligation to his hospital authority, writes that "Even before the Health Service was introduced a doctor holding an honorary appointment surely felt that he was *in the best sense* a servant of his hospital." (My italics.) Of course he did. But this was an emotional relationship not a legal one. He conducted himself and his work in such a way as not to tarnish, indeed to enhance, the reputation of a beloved institution of which he was proud, and today he is still activated by these considerations. The reputation of his hospital, however, was, and still is, essentially the collective professional reputation of himself, his colleagues, and his medical forbears. He was the servant of his hospital without being the servant of the management. We have always willingly accepted the directions of our clinical chiefs in regard to our clinical actions at the appropriate stages of our careers, and we have not stifled the initiative of our juniors by overweening directives. We ought to object strongly to professional directions from the hospital authorities influencing our actions in clinical matters; for these directions, based as they must be on caution and the avoidance of risk, must tend to have a stultifying effect upon the development of medicine.

Those, especially the young men, who feel that the authorities' acceptance of vicarious responsibility means a sharing of legal costs and damages should perhaps be reminded that a litigant's success in an action for professional negligence depends upon proof of the doctor's negligence. Doctors are no whit less liable to court proceedings and the attacks of counsel when the hospital authority is a co-defender (*anglice* defendant) than when he is sued alone.

If the last sentence in Sir Russell's letter means that the Health Ministers might be persuaded to accept that in the exercise of his clinical skill and judgment a doctor carried full and sole legal responsibility I am wholly with him. If he means anything short of this I am not. Furthermore acceptance of this principle by the Ministers would involve legislative action, since Her Majesty's Judges have ruled that under the present Acts the principle of the vicarious responsibility of the Ministers and the hospital authorities for the actions of their servants, the doctors, shall apply.

Other things flow from this, like the loss of the confidentiality of reports, the ownership by the Ministers of hospital case-records, and the assessment of part-time hospital staff under Income-tax Schedule E; but the most important is the loss of professional freedom. The campaign to restore this freedom, which has been begun in Scotland and which has been so notably supported by your leading articles, is not designed for any financial benefit to doctors, nor even for reasons of professional pride, but solely for what is believed to be the ultimate good of medicine, medical progress, and therefore the public interest.

Edinburgh. J. G. M. HAMILTON.

THROMBOPHLEBITIS AFTER INFUSIONS

SIR,—We welcome the attention drawn to thrombophlebitis by your leading article of Sept. 10. This is a most painful condition, in many instances more distressing to the patient than an operation wound. Irritant substances in the rubber tubing are largely responsible, and particularly severe are the irritant effects of rubbers vulcanised with tetramethylthiuramdisulphide, which can be readily identified by the fact that they inhibit the growth of bacteria. There are two points on which we would like to comment.

First, it would be dangerous to assume that plastic tubing could not contain harmful agents. Certain plastics contain plasticisers which are irritant to tissues. The refusal of some manufacturers to disclose all the constituents of which their tubings are compounded is a major difficulty in the selection of suitable tubing. We recommend that before any material is used it should be investigated by implanting it subcutaneously and examining the reaction of the surrounding tissues after a suitable interval, and that its effect in contact with tissue-cultures should also be examined.[1,2] When a giving set from which irritants cannot be leached out is available it will be possible to investigate the other factors which may contribute towards thrombophlebitis, such as tonicity and pH.

Secondly, we would like to emphasise that limiting the duration of each infusion to eight hours as laid down in your article is not the ultimate solution to the problem; it may be necessary at present, but we hope it is a temporary measure to be abandoned as soon as possible. To offer it as the final answer is an admission of defeat. Many patients need prolonged infusion, and with safe equipment and suitably compounded fluids it should be possible to run an infusion as long as necessary without risk. Such an infusion given into a large vein with a plastic catheter is much more comfortable to the patient than having a needle stuck into him daily, or eight-hourly as you advise. Moreover, frequent change of the infusion site, where this is possible, involves a great deal of work for the resident and nursing staff.

Haddenham, Bucks. R. P. C. HANDFIELD-JONES.
Birmingham. H. B. M. LEWIS.

NUMBERING OF FINGERS

SIR,—The council of the Medical Defence Union has considered a problem that arises from time to time in threatened or actual medical litigation. This problem has been created by the current nomenclature employed by anatomists and surgeons for the designation of the fingers. To do as many do—namely, to number the fingers 1, 2, 3, &c.—and to record in the clinical notes, e.g., that finger number 3 requires amputation is to set the stage for a serious surgical mishap. Now and again the surgeon reading the notes of the case at a later date before proceeding to operate has counted wrongly by choosing to regard the thumb as no. 1, instead of the index finger. In this way the wrong finger has been amputated or chosen for some other operation.

1. Parker, R. C., Morgan, J. F., Morton, H. J. *Proc. Soc. exp. Biol., N.Y.* 1951, **76**, 444.
2. MacDougall, J. D. P. *Nature, Lond.* 1953, **172**, 124.

It seems to the council of the Union that this serious mishap would be obviated if hospital medical officers when writing up clinical notes described the actual finger affected by adopting the designations "thumb," "index finger," "middle finger," "ring finger," and "little finger."

Medical Defence Union,
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ROBERT FORBES
Secretary.

GLUTAMIC ACID IN HEPATIC COMA

SIR,—We agree completely with Dr. Walshe [1] when he says that hepatic coma may arise from different causes. We treated ten comatose patients with 23 g. glutamic acid a day, together with the basic therapy of hepatic failure. Three patients have already survived for two years; two were cases of acute yellow atrophy. The third died of hæmorrhage due to œsophageal varices six months after the coma.[2 3]

There is certainly a disturbance of sulphur metabolism. Personal experiments on hepatic necrosis showed that the glutathione content of the liver and different organs is very low. The administration of glutamic acid prevents this decrease and seems to stimulate the synthesis of this tripeptide. The decrease in the blood is not as great as in the organs. Nevertheless in some cases of hepatic coma there was a decrease even of the blood-glutathione, which was temporarily corrected by administration of glutamic acid.[3]

But we would object to the method of determining pyruvic acid, α-ketoglutaric acid, and aceto-acetic acid. Instead of paper-strips we employed a triangular paper dipped in buffer ('Veronal' 0·1 *M*, pH 9) and dried before use. This permitted a far better separation of the 2·4-dinitrophenylhydrazines. So we have demonstrated a derivative of the phenylhydrazine just above the low spot of pyruvic acid. This spot is relatively water-soluble. When trying to remove the last trace of it we always lost some keto-acid. As Markees and Isherwood [4–6] pointed out, pyruvic acid gives two spots. But we also separated the two superior spots, which are isomers of phenylpyruvic acid. After ether extraction of the blood, they appeared on all the chromatograms. Ethyl-acetate extraction resulted in only a faint spot on the chromatogram. These findings have an important bearing on the quantitative assay of the different keto-acids.

J. DE GROOTE
P. DESCHEPPER
J. VANDENBROUCKE.

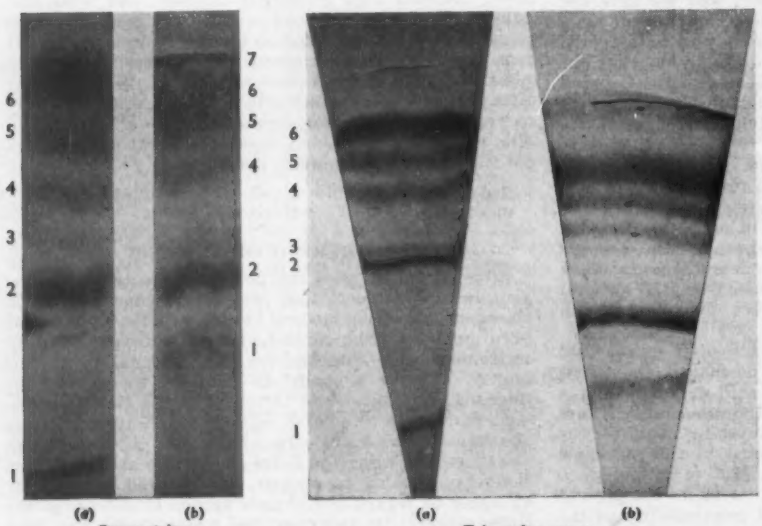
Laboratory of Physiopathology,
University of Louvain, Belgium.

1. Walshe, J. M. *Lancet*, 1955, i, 1235.
2. De Groote, J. *Belg. Tijdschr. Geneesk.* 1954, **10**, 230.
3. De Groote, J., Vandenbroucke, J. *Acta Gastro-ent. belg.* 1955, **18**, 209.
4. Markees, S. *Biochem. J.* 1954, **56**, 703.
5. Markees, S. *Experientia*, 1955, **11**, 205.
6. Isherwood, F. A., Cruickshank, D. A. *Nature, Lond.* 1954, **173**, 121.

RESERPINE THERAPY

SIR,—Ever since reserpine and similar alkaloids from rauwolfia have been used on a very large scale in the treatment of hypertension and neurotic symptoms in small doses, and in that of psychotic disorders in large doses, the effects of the drug have been studied extensively. Experimental work and clinical research demonstrated the physiological and psychological changes taking place during administration of the drug. Many patients treated with small doses for hypertension and neurotic disorders reported their feelings to their attending physicians. However, so far as I know, the abundant literature on reserpine contains no reports given by patients recovered from a psychosis treated with comparatively large doses. There is a characteristic discrepancy between the somatic and psychological effects experienced by the patient. The following report was given spontaneously by a 40-year-old school-teacher treated with parenterally administered doses of from 5 to 15 mg. reserpine daily for manic excitement with strong paranoid and aggressive features. He had had a poor childhood, but had not had psychotic disorders until after a head injury (fracture of left occipital bone) at 20. Since then he had had three major psychotic episodes described as manic excitements by mental hospitals where he was treated in Canada, France, and England. Here is his report:

"*The Effects of Reserpine (On Me).* This drug had one predominant physical reaction. It might be best described as causing tremendous physical exhaustion without inducing any mental weariness to go with it. Thus, about an hour after its administration I felt an almost overpowering desire to lie down, and once lying down, was unable to stay on the bed but after a couple of minutes, although still feeling the need for rest, had an equally uncontrollable urge to get up and move around. I remember particularly working in the kitchen one morning. I was peeling potatoes. I kept getting more and more tired and my hands moved more and more slowly. I cannot remember ever being more tired. When the potatoes were finished I sat down but almost immediately felt so restless that I had to get up and move around. While taking reserpine there would be periods when there was burning sensation in my head. I would see lights with my eyes closed, there would be a throbbing sensation in the top of my head and I would sometimes stagger with dizziness. There was always a feeling of a weight being upon my head as well as a sensation of internal pressure inside the head. I have no recollection whatsoever for a period of what must be a week or so when I was first given the drug. Very often I experienced extreme difficulty in catching my breath when I would get up from lying down or sitting. During the



Results of paper electrophoresis: (a) dipped and dried before use in veronal buffer (0·1 M, pH 9); (b) without buffer. Solvent: butonal/water/ethanol (5/4/1). Spots: 1, α-ketoglutaric acid; 2 and 4, pyruvic acid; 5 and 6, phenyl-pyruvic acid; 3 and 7, 2·4-dinitrophenylhydrazine derivatives.

period I spent in the admission ward I was living in a state of unreality with occasional lucid intervals. I imagined the place was hell and the attendants demons, some better than others. My moods would change very rapidly. One moment I would be extremely enraged at everyone and the next in a very silly state of elation. I do not ever remember any period of depression. It took a long time for these fits of anger and unreality to wear off. For some reason, which I am unable to explain, I did not emerge into a full realisation of reality till after the air encephalography test. After that the sensation of pressure in my head left me and I could see things and people for what they are."

Hospital for Mental Diseases, Brandon, Manitoba, Canada. MILO TYNDEL.

TRAINING THE DISTRICT NURSE

SIR,—The views expressed in your leading article (Sept. 10) deserve the wholehearted support of every general practitioner.

The Working Party majority seem to think that local authorities have been asked to take over the nursing service, not simply to provide one for the general practitioner to use. Also, there does not seem to be any good reason for the training to be done by local authorities any more than in the case of the midwife or health visitor. The nurses themselves strongly object to any reduction in the length of their training, as they fully realise that it is not the theoretical knowledge but practical experience that they need.

Surely more weight should be given to the opinions of bodies which have provided and used the service.

Plymouth. O. LL. LANDER.

STILBAMIDINE FOR TIC DOULOUREUX

SIR,—The administration of stilbamidine intravenously apparently is an effective, safe, and inexpensive method for the treatment of tic douloureux,[1 2] a condition for which therapy has been diversified and largely unsuccessful. When properly prepared and administered stilbamidine is not toxic except for a late chronic neuropathy. The progressive sensory changes of paræsthesia and hypalgesia usually confined to the face appear about two to five months after the administration of the drug. The mechanism of the neuropathy is not known.

Stilbamidine 0·15 g. is dissolved in 200 ml. of a 5% solution of glucose in distilled water. Since the drug in solution is markedly affected by even short exposure to light, the solution must be prepared immediately prior to its administration. The solution is given intravenously and must be given slowly to avoid a transient shock-like reaction associated with rapid administration of the drug. The course of treatment consisted of the injection of 0·15 g. of stilbamidine once daily for fourteen days.

Treatment was given to 14 outpatients, who were cautioned not to expose themselves unduly to sunlight. They carried on their normal occupations.

The cycle of clinical events after the start of treatment with stilbamidine is characteristic. The patients noted that the attacks of pain were less severe and less frequent from the fourth to the eighth day. Exacerbation of the pain, however, was usually noted during the first one to two months after the start of treatment. A gradual decrease in the severity and number of attacks followed. Complete freedom from pain occurred from two to four months after the inception of treatment. Mild paræsthesiæ consisting usually in pruritus and formication involving both sides of the face, appeared most often in about the third or fourth month. They appeared first and were more severe in intensity on the side of the face involved by the tic douloureux. The pruritus lasted for about one and a half months. The mild paræsthesiæ did not inconvenience the patients. The recognition of this clinical cycle is important; for otherwise discouragement may be felt during the first or second month, particularly after a good initial response. The delay in permanent improvement requires considerable patience on the part of both patient and doctor.

Of 16 patients with tic douloureux who were treated with stilbamidine, 14 had had previous treatment of some type. Excellent results were obtained in 15 patients and a good result in 1, with periods of freedom from pain ranging from four months to twenty-five months. The patients who obtained the lesser amounts of relief were treated only a short time ago. 15 patients were given one course of treatment, and only 1 required a second before a decrease in symptoms occurred. The corneal reflexes remained in all 16 patients, being brisk in 14, possibly blunted in 1, and slightly decreased in 1; the degree of impairment was not significant. In 1 patient the blunting of the corneal reflexes was due to a combination of a previous operation on the same side and the effect of the stilbamidine.

The Johns Hopkins Hospital, Baltimore, Maryland. GEORGE W. SMITH.
Veterans Administration Hospital, Fort Howard, Maryland. JOSEPH M. MILLER.

1. Smith, G. W., Miller, J. M. *Ann. intern. Med.* 1953, **38**, 335.
2. Smith, G. W., Miller, J. M. *Bull. Johns Hopk. Hosp.* 1955, **56**, 146.

ELECTROPHORESIS OF PLASMA-PROTEINS

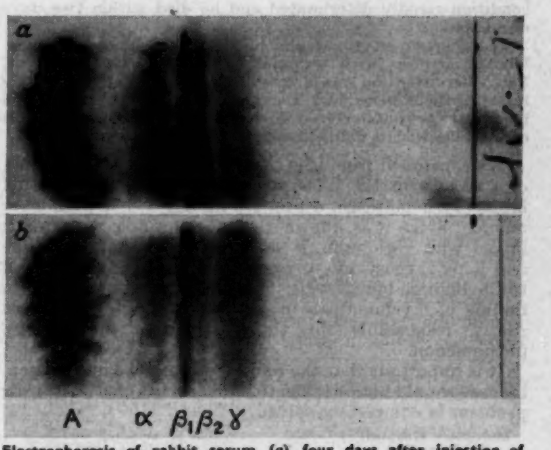
SIR,—I would like to add some remarks to Dr. Miltényi's letter of June 4 and to that of Dr. Christiansen (June 11).

In the serum of normal people the β_2-globulins isolated by paper electrophoresis form a substantially smaller part than the slightly faster moving β_1-globulins. A clear demonstration of β_2-globulins by this method is a relatively difficult procedure, but it is always possible. It is incorrect to assume, therefore, that the normal β-globulins usually travel as a single band, and that it is only with abnormal sera that the splitting into two fractions is observed.

We noted also that the increase of β_2-globulins was accompanied by a decrease in β_1-globulins. With the return of blood colloids to normal levels the ratio β_1/β_2 increases.[1] At present we are unable to explain the cause of this antagonistic behaviour of the β subfractions. These findings were confirmed experimentally.

Experimental dysproteinæmia was produced by means of a turpentine abscess in a rabbit. The serum-proteins were examined electrophoretically in the usual way several times during the activity and healing of the abscess. In contrast to human serum, the α-globulins did not split under these experimental conditions. The β_2-globulin fraction increased in the

1. Wiedermann, D. *Schweiz. med. Wschr.* 1954, **84**, 1367.



Electrophoresis of rabbit serum (a) four days after injection of turpentine and (b) twenty-two days after injection of turpentine.

acute phase, while with α-globulins it decreased considerably. β_1-globulins, on the other hand, increased notably during healing (see accompanying figure).

It was interesting to compare these results with those of the flocculation methods, modified in our department for investigation of the serum-proteins of rabbits. The increase in the α-globulin and β_2-globulin fractions manifested itself by an increase in the acid-precipitable globulin (A.P.G.) test (modified after Greenspan). The decrease of γ-globulin in the acute phase was evident not only on electrophoresis, but even in our modification of the cadmium-sulphate test (Pospíšil, personal communication). On the other hand, flocculation of total lipoids in the original modification of the thymol test, carried out in pH 4·2,[2] showed lowered values when α-globulin and β_2-globulin increased, thus raising the question of the importance of lipoids for the changes in these fractions in rabbits.

Department of Experimental Pathology,
Masaryk University, Brno,
Czechoslovakia. D. WIEDERMANN.

THE "L.E.-CELL" PHENOMENON IN ACTIVE CHRONIC VIRAL HEPATITIS

SIR,—The report by Dr. Joske and Dr. King (Sept. 3) prompts me to mention a similar case in which L.E. cells were found in association with liver disease and in the absence of lupus erythematosus.

A man, aged 50, was first seen in July, 1953, with a purpuric eruption on the legs. There were also transient tender nodules on the legs which may have been due to an existing foot ringworm. He had a recent history of loss of appetite, dislike of fatty foods, and pale stools. He had never been jaundiced, had never received a blood-transfusion, and had never been exposed to occupational poisons.

On admission to hospital the relevant abnormalities were facial telangiectases, liver enlargement (4 finger-breadths), spleen just palpable, no jaundice.

Plasma-albumin was 3·3 g. per 100 ml., plasma-globulin 5·0 g. per 100 ml., serum-bilirubin 0·8 mg. per 100 ml., alkaline phosphatase 13 units, thymol turbidity 16 units, colloidal gold 5 units, cephalin-cholesterol 4 units.

L.E. cells were found in large numbers in the blood. In view of this, particular care was taken to search for clinical signs of lupus erythematosus, but there were none; the white blood-cell count ranged from 14,700 to 4500 per c.mm.; the erythrocyte-sedimentation rate was normal; the blood Wassermann reaction was negative.

The patient was discharged from hospital and readmitted a month later under the care of Prof. Alan Kekwick with increasing jaundice and intermittent abdominal pain and vomiting of a week's duration. At this time there was also considerable ascites. The white blood-cell count was 15,000 per c.mm. and again L.E. cells were found in the blood. His condition rapidly deteriorated and he died within two days of admission.

Post-mortem examination confirmed the diagnosis of multilobular cirrhosis with terminal acute necrosis of the liver. Particular attention was directed to the possibility of systemic lupus erythematosus, but no evidence of this was found. The bone-marrow contained a diffuse infiltration with plasma-cells compatible with a diffuse type of myelomatosis.

We concluded from this case that, although the finding of L.E. cells in the blood usually indicates disseminated lupus erythematosus, a positive finding is not pathognomonic. Since it is known that the serum L.E. factor is linked with γ-globulin, it seems possible that, as Joske and King suggest, in our patient the reaction was related to the high globulin levels. The unexpected post-mortem finding of myelomatosis in our case may also have been partly responsible for the production of the L.E. phenomenon.

It is important that the finding of L.E. cells in a particular case should not be taken to indicate that the diagnostic problem is completely solved.

Middlesex Hospital,
London, W.1. F. RAY BETTLEY.

2. Pospíšil, M. *Vnitřní lékarství*, 1955, **1**, 30.

REGISTRARS

SIR,—Last week's letters on the registrar problem seem to overlook an important factor concerning the entry into general practice. This factor is age. There are at present many N.H.S. practices which support senior partners of 70 plus, and in some cases 80. Surely it would be reasonable for the Ministry to set a retiring age of 70. There would then be many more vacancies in general practice.

EX-REGISTRAR GENERAL PRACTITIONER.

CHLORPROMAZINE: A SEROTONIN ANTAGONIST?

SIR,—Some years ago I pointed out that several anti-histamines inhibited the amines tyramine, tryptamine, and phenylethylamine.[1] On the basis of these findings I suggested that more potent 5-hydroxytryptamine (serotonin) antagonists could be found among diamines of $R_2 : N.(CH_2)_3.N : R_2$ structure. When chlorpromazine became available therefore we investigated its anti-serotonin action.

A new interest was added to this question when Gaddum [2] discovered that lysergic acid diethylamide was the most active anti-serotonin agent hitherto known. The possible rôle of serotonin and its importance in mental disturbances have also been discussed.[3,4] It seemed rational to investigate the anti-serotonin action of chlorpromazine, although its effect in psychiatric cases is not the same as that of L.S.D.

In spinal cats we found that the vasopressor effect of 20–40 μg. per kg. serotonin (expressed as serotonin creatinine sulphate) was nearly completely blocked by 1·0 mg. per kg. chlorpromazine. On isolated rat uteri the effect of serotonin (0·05–1·0 μg. per ml. of bath) was completely inhibited by the same concentration of chlorpromazine.

These preliminary results suggest that chlorpromazine is one of the most potent anti-serotonin drugs. Its effect in both experiments was long-lasting.

Further investigations will be necessary to prove the hypothesis that the mental effects of some drugs are related to their anti-serotonin effect. The striking anti-serotonin effect of chlorpromazine, on the other hand, may explain why this drug so effectively counteracts various shock symptoms in which serotonin might be involved.[5]

Department of Pharmacology,
Research Institute of the
Pharmaceutical Industry,
Budapest, Hungary. L. GYERMEK.

GASTRIC SECRETION IN SIMMONDS'S DISEASE

SIR,—In a review of 595 cases of Simmonds's disease, Escamilla and Lisser [6] found that gastric acidity was low or absent in 85% of those patients in whom the diagnosis had been confirmed by pathological examination. More than half of these patients had gastro-intestinal symptoms. The following case is of interest because the secretion of acid and the gastric mucosa appear to have been restored to normal during hormone treatment for hypopituitarism.

A housewife, aged 51, was admitted in March, 1953, for investigation following attacks of vomiting over a period of four months. She had had a severe postpartum hæmorrhage 22 years previously, which was followed by amenorrhœa and loss of pubic and axillary hair. She was thin and appeared disinterested in her condition. The blood-pressure was 120/55 mm. Hg, pulse 100 per min., Hb 12·3 g. per 100 ml., and 17-ketosteroid excretion nil. Gruel and histamine (0·5 mg.) test-meals showed absence of free gastric acid.

1. Gyermek, L. *Acta physiol. Acad. Sci. Hung.* 1953, **4**, 323.
2. Gaddum, J. H. *J. Physiol.* 1953, **121**, 15.
3. Gaddum, J. H. Ciba Foundation Symposium on Hypertension. London, 1954.
4. Page, I. H. *Physiol. Rev.* 1954, **34**, 563.
5. Page, I. H. *Amer. Heart J.* 1948, **38**, 1.
6. Escamilla, R. F., Lisser, H. *J. clin. Endocrin.* 1942, **2**, 65.

Gastroscopy (Prof. H. W. Rodgers) showed a gross, diffuse, foldless atrophy of the gastric mucosa.

Treatment was then started with deoxycortone acetate (200 mg. implant) and thyroid extract (gr. 1) (65 mg.) daily. There was some improvement in the patient's general condition, but improvement was much more rapid when cortisone (12·5 mg. daily) was given and deoxycortone was discontinued.

Eight months after commencing cortisone, histamine and gruel test-meals showed that free gastric acid had returned; in the gruel test-meal the free-acid curve rose normally to 40 clinical units. Gastroscopy on this occasion showed a mucosa of normal thickness and colour, but with only very small folds. The Hb level was 13·5 g. per 100 ml.

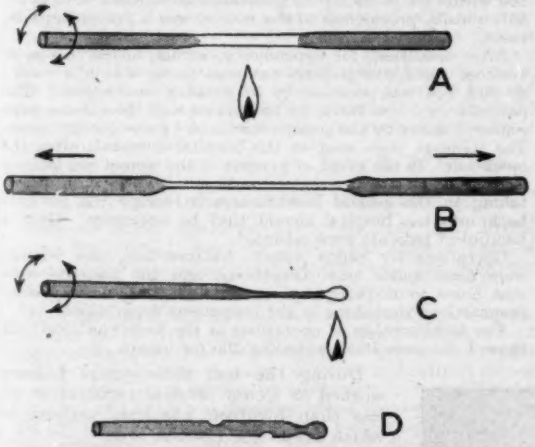
It seems probable that the restoration of gastric secretion in this patient was due to the action of cortisone rather than to the action of thyroid extract. Sandweiss,[7] on the evidence available, did not believe that there was a definite relationship between the thyroid gland and peptic ulceration, and Hardt [8] found a decrease in postcibal gastric secretion in the dog after giving desiccated thyroid. On the other hand, it is known that cortisone will largely restore the gastric secretion in the hypophysectomised rat [9]; and Stempien and Dagradi [10] have reported the restoration of gastric secretion following cortisone therapy in a patient with Addison's disease.

Department of Surgery,
Queen's University of Belfast. JAMES KYLE.

OLIVE-TIPPED POLYTHENE URETERIC AND VENOUS CATHETERS

SIR,—Non-irritant 'Polythene' ester is a good material for ureteric and venous catheters that must remain for a long time in the body.

Polythene tube size 3, with an internal diameter of 1·6 mm., is good for these purposes; but the advancing end of such a tube, even when rounded or bevelled, may fail to pass. Alternatively in passing it may damage or



even penetrate the wall.[11] The following method of giving an olive tip to the tube may help those who have experienced these difficulties.

The tube is carefully heated over a small flame until a short segment loses its pearly texture and becomes transparent (A). The tube is then removed from the flame and drawn into a thick capillary like a Pasteur pipette (B). This capillary segment is severed in the middle and its cut end is again heated over the flame. A molten globule of polythene forms at the end, and, retracting towards the taper, increases in size (C). Kneading with the fingers while the tip is still warm produces an elegant olive shape.

Side-holes are cut with pointed scissors (D) and lengths along the tube are marked as required. After chemical sterilisation the catheter is ready for use.

Thus modified, the catheters are easy to pass up ureters obstructed by growth, and they slide smoothly up peripheral veins into the great veins without damaging their walls.

Radcliffe Infirmary,
Oxford. A. M. N. GARDNER.

ANTIBIOTIC-RESISTANT STAPHYLOCOCCAL INFECTIONS

SIR,—The time and effort Dr. Barber and Dr. Burston have spent on their inquiry, described in your issue of Sept. 17, were well worth while. Their findings of numerous staphylococcal strains resistant to penicillin, streptomycin, oxytetracycline, or chloramphenicol, and, more important still, of almost 25% of all strains resistant simultaneously to penicillin, streptomycin, and the tetracyclines, are a timely reminder to clinicians to use all antibiotics with the greatest care and regard to the long-term usefulness of these drugs. It might not be a bad plan if clinical bacteriologists were consulted personally, and brought to the bedside, in every case where a patient is about to receive antibiotic treatment.

In one respect, however, the article by Dr. Barber and Dr. Burston is open to question. They do not seem to consider reducing the incidence of resistant strains by rational combination of antibacterial drugs. Yet it has been generally accepted, in the treatment of pulmonary tuberculosis, that combination of streptomycin with *p*-aminosalicylic acid and/or isoniazid will avert, or at least postpone, the emergence of resistant strains. The genetic principle involved was formulated by Demerec [1] in 1948 as follows:

> "Theoretically, the most effective way of preventing the origin of resistant strains of bacteria is the use in clinical treatment of a mixture of two antibiotics when such are available, that effect the same pathogen but are independent in their actions. . . . If such a mixture of two antibiotics is used, then only bacteria that are resistant to both can survive the treatment and form resistant strains. Such bacteria would be exceedingly rare."

Attention was drawn in this country to Demerec's principle by Zinnemann,[2] who advocated the combined use of penicillin, streptomycin, and one of the sulphonamides in meningitis due to *Hæmophilus influenzæ*. Apart from avoiding resistance, combination of antibacterial drugs is likely to result in synergic action on the infecting micro-organisms.[3–5]

Although the mode of action of most antibiotic drugs is as yet unknown, it has been found that streptomycin on the one hand [6] and the sulphonamides on the other [7] exert their action on bacteria in ways completely different from that of all other antibiotics. On first principles, therefore, streptomycin and/or the sulphonamides should be combined with any one of the other antibiotics.

These considerations have been given in some detail, for I do not entirely agree with the suggestion by Barber and Burston that the use of erythromycin should be rigidly curtailed and that this drug should be used only for infections resistant to all other antibiotics. Next to chloramphenicol,[8] which can no longer be administered for long periods, erythromycin is one of the most effective antibiotics in the long-term treatment of chronic pulmonary infections due to *H. influenzæ*. We have used erythromycin along with the tetracyclines, in combination with a sulphonamide, for quite some time now. Accord-

7. Sandweiss, D. J. Peptic Ulcer. Philadelphia and London, 1951.
8. Hardt, L. L. J. *Amer. J. Physiol.* 1916, **40**, 314.
9. Kyle, J. Observations to be published.
10. Stempien, S. J., Dagradi, A. *Gastroenterology*, 1954, **27**, 358.
11. Doane, J. C., Paul, A. J., Sohn, W. J. *J. Amer. med. Ass.* 1953, **151**, 384.

1. Demerec, M. *J. Bact.* 1948, **56**, 63.
2. Zinnemann, K. *Brit. med. J.* 1950, ii, 705.
3. Ungar, J. *Nature, Lond.* 1943, **152**, 245.
4. Chain, E., Duthie, E. S. *Lancet*, 1945, i, 652.
5. Thomas, J. C., Hayes, W. *J. Hyg., Camb.* 1947, **45**, 313.
6. Garrod, L. P. *Brit. med. J.* 1945, i, 107.
7. Woods, D. D. *Brit. J. exp. Path.* 1940, **21**, 74.
8. Zinnemann, K. *Brit. med. J.* 1953, ii, 1069.

ing to the authors' recommendations, if I understand them correctly, we have done the wrong thing; for we might have produced erythromycin-resistant staphylococci while treating *H. influenzæ* infections. Yet, we have reason to believe that by combining erythromycin with an effective sulphonamide in intermittent treatment we have minimised this danger over long periods.

The combined use of antibacterial drugs, far from being blunderbuss therapy, will in the long run be our only hope of winning the "neck-and-neck race" with the adaptability of bacteria.

Department of Medicine,
University of Leeds. K. ZINNEMANN.

NURSING BY THE MOTHER

SIR,—Last year in a paper on Elimination of Hospital Cross-infection: Nursing by the Mother[1] and in subsequent correspondence it was claimed that this system of nursing, by abolishing the pool of infection in a common ward, and by preventing transference from patient to nurse to patient, not only gave more certain results but eliminated the effects of even slight infection from the operation wound and that this could be judged best by the absence of even slight scar tissue or suture marks especially in delicate infant tissues.

A very good test subject is a bad hare-lip case, because the functional and cosmetic results are so obvious and "marks" from infection are so readily seen in good clinical photographs. Other advantages claimed were that by mother-nursing (in a single room) both the operative and nursing procedures could be very much simplified with advantage and the time spent in hospital reduced. The accompanying figure shows a baby girl who was admitted (with her mother) because of a bilateral harelip at 14 weeks of age. The operative and nursing procedures, in brief, were as follows:

Full feed 5 hours prior to operation; glucose saline rectal drip established before start of operation, 5 oz. given and all absorbed; no gloves worn at operation by surgeon or sister; no intratracheal anæsthesia (which too often causes post-operative troubles). At the conclusion of the operation a thin film of penicillin ointment was smeared over the lip with my bare finger, otherwise no dressing at all was applied (all sutures visible); no strapping, no Logan's bow, no restraints used except flannel bands, $1^1/_2 \times 8$ in., pinned round each wrist and to the napkin (thus the baby could play with her fingers but not put them in her mouth). Duration of operation 1 hr. 15 min. An hour later the patient was returned to the mother, who then took full charge. Sips of glucose and milk in graduated strengths and amounts were given by spoon hourly, starting 2 hr. after operation and continuing through the night as often as the baby woke until next morning she was taking 6 oz. of her normal milk formula by spoon-feeding. There was no postoperative reaction and no postoperative sedation was necessary. As can be seen from the post-operative photograph, there is no evidence of even a trace of infection, and function is very good. No antibiotics were used parenterally at any time. The mother did everything for the patient except removal of the sutures, which was done in the theatre under anæsthesia. The patient left hospital on the 8th day after operation.

1. Pickerill, C. M., Pickerill, H. P. *Lancet*, 1954, i, 425.

This supports Murray and Calman's[2] findings that an infant carries immunity to its mother's organisms; for the mother wore neither mask, gown, nor gloves. It would seem that there may have been a tendency to regard surgical ritual as inviolate and that we may rely on it too much, not always to the advantage of the patient. It is surely more logical to strike at the source of infection than to ignore it and then have to take great precautions to prevent its effects, and not always successfully but with certain loss of nimbleness of one's fingers. There are three other common effects of infection from the pool of organisms in an open ward, which can be seen and recorded—namely, acquired respiratory-tract infection, gastro-enteritis, and sore or ulcerated buttocks. Since the paper referred to above was written two years ago, no case of any of these infections has occurred.

Bassam Hospital,
near Wellington, New Zealand. CECILY M. PICKERILL.

EARLY AMBULATION

SIR,—In the year 1944–45, as resident surgical officer in a 100-bed non-teaching voluntary hospital in Lancashire, I was confronted with a waiting-list of over 600. Of these, 300 were general surgical cases. Little more than two-thirds of the beds were in use, and about 60 of these were surgical beds.

Having received the consent of the surgeons and nursing and administrative staff, and the promised coöperation of the general practitioners, the waiting-list was reduced to under 200 within six months; no general surgical cases were left—only tonsils, procidentia of the uterus, and a few orthopædic cases.

After operations for appendicitis, hernia, hæmorrhoids, or varicose veins, the patient was sent home within a week; so each bed was occupied by 52 patients in the year. The patients were sent home by ambulance and the sutures were removed either by the private doctor or by the district nurse. The patients were seen at the hospital a month after the operation. In the event of pyrexia or the wound not looking healthy, the patients remained in hospital. I gave an undertaking to the general practitioners to accept the patients back into the hospital should that be necessary. Only a handful of patients were returned.

Operations for hallux valgus, hammer-toes, and bursitis were done under local anæsthesia, and the patients were sent home immediately by ambulance. The two-day skin-preparations were done in the outpatient department.

The total number of operations in the year was 2500. Of these I did over 1000, including 200 for hernia.

During the last three years I have worked as locum surgical registrar in no less than eighteen hospitals, sixteen of which are in the London area.

In only one of these hospitals (a large one in Hampshire) was there a substantial waiting-list of over 1000 general surgical cases. The reason for the large waiting-list was similar to that named by Mr. Farquharson (Sept. 10)—that operations were done as a priority on patients with carcinoma. In many cases the operation amounted to a futile laparotomy. The town being popular with old people, the incidence of cancer was on the high side.

In another hospital (in the London area) there was a waiting-list of 200 general surgical cases.

In all the other hospitals there were practically no waiting-lists for general surgery. The operating sessions were at times

2. Murray, J., Calman, R. M. *Brit. med. J.* 1953, i, 13.

made up of minor operations, such as circumcisions, cystoscopies, and sigmoidoscopies. There were times when no operations were done at all.

It is my impression that, though local anæsthesia is practised in England as a routine in old people with strangulated herniæ and in suprapubic cystotomies, younger patients would not take to it as well as the hardier stock across the Border.

I can see one benefit from not keeping the patient in hospital after operation. It might reduce the number of new addicts to barbiturates and other hypnotic addicts. In many cases hospitals are responsible for initiating such addiction.

London, N.W.11. I. GOTTLIEB.

ON EXPELLING TAPEWORMS WITH MEPACRINE

SIR,—I was interested to read Dr. Seaton's article last week. Personally, I have never failed to remove tapeworms complete with scolex, using filix mas, provided 2 drachms of sodium bicarbonate, dissolved in a minimum quantity of water, is first given on an empty stomach.

Those of us who have seen tapeworms in situ in the lower animals know how the scolex is always surrounded by a thick layer of mucus. The administration of sodium bicarbonate presumably dissolves the mucus and allows the filix mas to act directly on it. On one occasion three tapeworms, complete with scolices, were removed from one patient at the same time.

London, W.1. IDRIS JONES.

SIR,—Dr. Seaton's article interests me. I have not had a case of tapeworm to treat for some years; but with male fern I had no disappointments—and no vomiting or other complication—and I evicted my own unwelcome guest without stopping work except for one Sunday.

The method was to take no solid food on Thursday, Friday, and Saturday. I drank fluid magnesia thrice daily, and went into a nursing-home on Saturday evening with a dose of emulsion as advised many years ago by the late Dr. Burney Yeo. The principle is to eliminate mucus, starve the worm, and let him have a knockout when his resistance is low and there is no longer a layer of mucus protecting the all-important head. No aperient was needed, and nine yards of worm came away with the head.

Swindon, Wilts. R. P. BEATTY.

ILIO-INGUINAL BLOCK DISSECTION

SIR,—I must apologise for perturbing Dr. Rivlin (Sept. 24), but I think he draws too close a parallel between the operation for varicose veins and that for clearance of the groin.

It is quite true that an incision for Trendelenburg's operation will heal by first intention . . . even if the superficial epigastric and superficial external pudendal arteries are divided at their origins. Why shouldn't it? The undisturbed tissues on either side of the wound are adequately nourished by the collateral circulation via the branches of the divided arteries, and by the third spoke of my stupid little wheel—the superficial circumflex iliac artery. In radical dissection of the groin, however, *all three* vessels are divided both near their origins and at the periphery: divided, as it were, at the hub and at the rim. All intermediate branches are similarly divided, whether the flaps are thick or thin, and there can be little doubt that the blood-supply to the skin at the centre of the operative field is a trifle precarious.

Dr. Rivlin no doubt bases his comments on a careful scrutiny of many of these wounds, and he may agree that when a standard near-vertical incision is made, an area of skin (variable in extent, but never very large and always much less than the total area over which the flaps have been thinly raised) passes through all the stages of ischæmic gangrene, being finally delineated by a well-marked line of demarcation. This happens whether a layer of subcutaneous fat is included in the flap or not. It is the separation of this slough and the resultant granulation, which delays healing.

Since reading Mr. Stanley Lee's excellent article (Sept. 10), I have dissected the groin in another female patient. For reasons which are not germane to the present argument I did not wish to remove the iliac nodes, and was therefore reluctant to use Mr. Lee's extended incision. I did, however, adopt one of his principles and started the operation by outlining an ellipse of skin roughly equal in size and position to the area which usually becomes gangrenous. This ellipse was included in the tissue removed, after the manner of a mastectomy, and it was gratifying to find at the end of the operation that the skin edges came together without tension—no doubt because of the large mass of tissue removed. Any "dead space," another mythical bugbear of this operation, was obliterated by the ingenious, if rather old-fashioned, manœuvre of applying a pad and bandage. The flaps were very thin, but the wound is healing by first intention.

It seems that a thin flap of skin will survive if its blood-supply is adequate, whereas the fattest leg will mortify if the life-giving fluid is cut off. I hope Dr. Rivlin will not be blinded by this dazzling glimpse of the obvious.

South Mimms, Herts. V. J. DOWNIE.

SILICONE RUBBER IN SURGERY

SIR,—The use of silicone rubber tubing in neurosurgical procedures was discussed in a preliminary communication which you published for me last year.[1] Its physical properties were considered excellent, especially that of heat resistance, which facilitates repeated sterilisations. Unfortunately, however, our further experiences suggest that it can give rise to a particular toxic reaction.

In the past 15 months twelve patients have been under observation, in whom altogether eighteen silicone rubber tubes have been introduced. With one exception these have been cases of obstructive hydrocephalus, where various operations have short-circuited the obstruction by passing a tube from the ventricles to the subarachnoid space. Our first patient died suddenly elsewhere, a month after operation. The remainder have made satisfactory recoveries, and all tubes remain patent in the sense that no relapses due to disturbances of intracranial pressure have occurred.

It is to the postoperative period that attention must be drawn; for, although convalescence was uneventful in half of our patients, there was a delayed meningitic reaction in the other half.

The most striking feature of these reactions was their initial appearance, in all six cases, on either the 16th or 17th day after operation. In one patient serial lumbar punctures showed a maximum pleocytosis (144 cells per c.mm., mostly lymphocytes) and protein increase (150 mg. per 100 ml.) at the 16th day without a clinical disturbance. In the remaining five, a rise in temperature and meningismus for 1–2 weeks accompanied the cerebrospinal-fluid changes—which ranged from 75 to 2000 cells per c.mm. (mostly polymorphs) and from 80 to 300 mg. of protein per 100 ml. From the C.S.F. of each of the two most ill patients a *Staphylococcus albus* was grown. In one of these cases its repeated recovery from the C.S.F. indicated that the organism was at least partly responsible for the meningitis. In the other we regarded it as a contaminant.

Two patients had recurrent mild attacks of meningeal irritation before discharge from hospital. The time between operation and returning home averaged 1 month in those six who did not develop signs of meningeal reaction in the immediate postoperative period; it averaged 2 months in those who did.

Though silicone rubber retains its surface effect of water repellency, it does in fact absorb water, owing to the mineral filler used in its manufacture. The degree of absorption depends on the filler. It is known that certain types are responsible for an increase in weight of as much as 50% when the rubber is immersed in water for 7–8 months. May the delayed reactions we have observed

1. Dimant, S. *Lancet*, 1954, ii, 533.

be related to this absorption of water? It is certainly possible that a slow diffusion from this material of a toxic substance—perhaps benzoic acid derived from the vulcanising agent—could provoke a meningeal reaction when it has reached a toxic concentration in the C.S.F. It should also be pointed out that examination of the tubes recovered from the one fatality in this series revealed fine cracks in the outer surface. This followed a period of a month in vivo. In vitro no such alteration has been reproduced; so this effect is probably due to tissue reaction.

These results indicate that a delayed reaction may be caused by silicone rubber tubes within the central nervous system. They suggest too that tissue reaction may in turn affect their durability. The neurosurgical use of the original silicone tubes has consequently been suspended in this department while laboratory experiments are proceeding with silicone rubber of altered composition.

Department of Neurosurgery,
Royal Infirmary,
Manchester, 13. STEVENS DIMANT.

CALCIFICATION WITHIN THE LIVER

SIR,—I was interested in the article on this subject by Dr. Smallwood and his colleagues (Aug. 20). Calcification of liver is uncommon, and hydatid disease is the commonest cause. I should like to report the following case.

An old man of 70 was admitted to a surgical ward with abdominal pain due to a femoral hernia. For the past four years he had had pain in the epigastrium after food, which was relieved by alkalis. Recently he had lost some weight. He had had a "bad chest" for many years, and increasing dyspnœa had gradually developed. For most of his life he had worked in factories. In the 1914–18 war he had been at the Dardanelles, where he had no illness. He had no pets.

On examination he was thin and dyspnœic, with tenderness all over the abdomen and large visible veins on the abdominal wall. The liver was grossly enlarged, hard but not tender. The spleen was moderately enlarged.

Investigations.—Straight radiography of the abdomen showed a calcified ring shadow in the gall-bladder region (fig. 1). Barium meal revealed a shallow gastric ulcer in the upper part of the lesser curve. Barium swallow: no œsophageal varices. Radiographic examination of the chest showed an opacity in the upper mediastinum. Alkaline phosphatase 18 units, thymol turbidity 2·5 units. Total plasma-proteins 7·5 g. (albumin 3·5 g., globulin 4·0 g.) per 100 ml.

Operation.—The hernia was reduced, but no other treatment was advised.

Readmission.—A week after discharge the patient was readmitted to a medical ward with profuse hæmatemesis, and he died in coma a few days later.

Necropsy showed a large carcinoma related to the right bronchus. The stomach contained a large ulcer, about 5 cm.

Fig. 1.

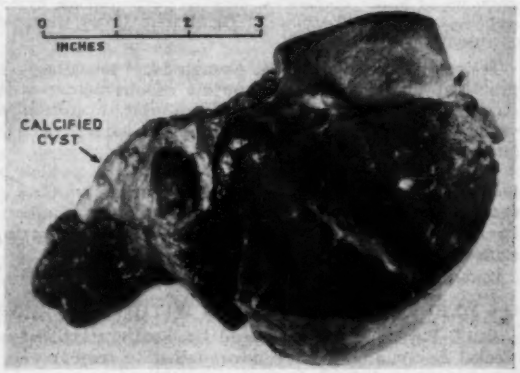


Fig. 2.

in diameter, penetrating the stomach wall and adhering to the tail of the pancreas; and there was another small ulcer beside this. Numerous adhesions were present between loops of intestine, and there was an abscess under the left diaphragm. The liver was enlarged and its capsule was thickened. The liver contained a cyst, 5 × 2½ cm., to the right of the gall-bladder (fig. 2). The wall of this cyst was calcified. Its contents, which were yellow, were found microscopically to include *Cysticercus echinococcus*.

I am grateful to Dr. J. L. Taylor for permission to publish this case.

Birch Hill Hospital,
Rochdale. P. S. MUKHERJI.

STAFFING THE TRANSFUSION SERVICE

SIR,—Having been abroad for some little time, I have till now missed the sounds of battle. You, Sir, put me to considerable inconvenience with your issue of Sept. 3, which I had to hide securely from the members of my staff. I wanted to prevent them from leaving, thus following the suggestion which Dr. Discombe made for any intelligent person "who by a mischance . . . entered that field." Conceding, however, for a moment that Dr. Discombe is right and that no intelligent person will stay in the service (I take it he includes medical and scientific staff) I feel that the Transfusion Service in this country would not seem to be doing too badly, in spite of the half-wits running it. The fact that several countries have built up a service on the pattern of the British service is a compliment which possibly balances out the adverse criticism of the service by Dr. Discombe. Dr. Discombe is obviously dissatisfied with the way the affairs of the service are conducted, but I fail to see what he wants us to do. Nobody would dispute his contention that it is the primary duty of the Transfusion Service to provide blood, and if he cares to look at the statistics, as Dr. Bowley has already suggested (Aug. 6), he will see that there is quite an amount of blood forthcoming. In all likelihood it is correct to say that during the existence of the national service, no-one in this country has died because no blood could be found for him or her. It would, however, appear to me that Dr. Discombe, never having been in charge of a transfusion centre or having been responsible for the production of large numbers of bottles of blood, does not see the problems in the right perspective. Apparently Dr. Discombe would prefer a transfusion service to be something like a dairy with a weekly blood round; but I am sure that he realises that not even a dairy could provide a safe product without an ancillary laboratory, and the higher the standard of the laboratory, the safer, broadly speaking, will be the product. Why then does Dr. Discombe not concede to the Transfusion Service activities which he probably encourages in a dairy? Does he really want us to degenerate into blood-collecting

units which thus would lose not only their standards but also their reputation both at home and abroad?

The standard can be kept up only if staff can be trained efficiently. If we refrained altogether from doing antenatal work or did too little of it, or did no other work but blood collecting, grouping, and typing, the work would indeed become dull and uninspiring. I suggest, Sir, that what Dr. Discombe claims to be the fact at present—namely, that every intelligent person leaves the service—would then come about.

There is one statement in Dr. Discombe's letter which I cannot understand at all. He states "... a field in which promotion is slow and from which transfer is likely to be difficult because of this specialisation." Just why is promotion slower in the Transfusion Service than in pathological laboratories? The grading is the same throughout the country, and vacancies in the Transfusion Service laboratories are bound to occur. With regard to transfer, this I feel is entirely untrue. Every technician trained in the Transfusion Service—and by trained, I mean the type of training which would satisfy the director of the centre—can be absolutely certain of getting immediate employment in any pathological laboratory. My experience is that pathologists are only too keen to get technicians trained in a transfusion centre. The opposite might not always be true.

If it be true that only laboratories performing antenatal tests are capable of doing proper cross-matches, the policy in the whole country should be changed. It will surely not have escaped Dr. Discombe's notice that there are a large number of hospitals up and down the country which have a most efficient pathological service which includes efficient blood-grouping and cross-matching but whose staff do not do any antenatal tests at all. I cannot see how a children's hospital, an accident hospital, or for that matter any specialised hospital could come across any antenatal specimens in their routine unless some "charitable" person would give them some antenatal work to do. I am, however, certain that the pathologists in these hospitals would not like to undertake any antenatal work at all. In Dr. Discombe's opinion, these people would never attain the standards which Dr. Discombe postulates for cross-matching tests. It is a moot question whether the techniques applicable to cross-matching and antenatal work are identical. From my experience I would suggest, Sir, that they are not. Though the end-result of all serological tests is agglutination or lack of it, the problems in antenatal work and cross-matching are different.

Dr. Discombe mentioned that he studies about 200 antenatal blood samples per month and says that he screens 30–40 sera for antibodies and that he titres out 5–10 sera. Does he really mean to say that only 15–20% of all the samples submitted to his laboratory are screened for antibody content? It is a practice in most laboratories dealing with antenatal specimens to screen every one, having regard not only to the common antibodies but also to the rarer antibodies, as they may be equally important clinically. To a mother it is quite immaterial whether her child died on account of hæmolytic disease of the newborn caused by an anti-rhesus antibody or by an anti-Kell or an immune α. The screening of every antenatal sample and the full investigation involves, of course, very much more work than just "screening" selected samples. It speaks highly for Dr. Discombe that he must have this "solid block of work" to make his technicians and himself confident in their reagents and techniques. It is, however, conceivable that he may gain by shedding some work which is not his primary duty and letting that be done in a different laboratory where it could be undertaken equally efficiently. Dr. Discombe is indeed fortunate if he can combine both activities without one of them suffering.

Dr. Discombe admits in the last paragraph of his letter that his scheme would involve some increase in the use of sera and man-power. I suggest, Sir, that we can ill afford to waste either. May I suggest that there are regions where there is enough serum to go round for the essential duties performed by all pathological laboratories in the region, and that even the very burning problem of man-power can be solved if there is harmonious coöperation between the pathological laboratories and the transfusion centre. It is perhaps not pertaining to this correspondence, but I would be obliged to you, Sir, if you would allow me to finish this far too long letter by thanking my colleagues in my own region for the help and understanding which they have accorded me all the time I have been responsible for the service in Birmingham.

Birmingham. W. WEINER.

Diary of the Week

OCT. 2 TO 8

Monday, 3rd

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, S.E.5
5.30 P.M. Dr. F. Stengel: first of five lecture-demonstrations.

Tuesday, 4th

UNIVERSITY OF LONDON
5 P.M. (Middlesex Hospital Medical School, W.1.) Dr. W. S. McCulloch (Massachusetts Institute of Technology), Dr. Patrick Wall (Harvard University and M.I.T.): Plotting of Pathways in the Central Nervous System. Action of Strychnine.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. C. O. Carter: Principles of Genetics.

Wednesday, 5th

UNIVERSITY OF LONDON
5 P.M. (Middlesex Hospital Medical School, W.1.) Dr. McCulloch, Dr. Wall: Fate of Afferent Impulses in the Central Nervous System. Reflex Inhibition.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. O. Oliver: Pyogenic Cocci in Skin Diseases.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. F. H. Young: Pathogenesis of Tuberculosis. (First of three lectures.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.15 P.M. *History of Medicine.* Prof. Walter Artelt (Frankfurt): The Doctor makes his Rounds.
LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P.M. Prof. J. Trueta: Ætiopathology of Osteoarthritis. (Hugh Owen Thomas lecture.)
MIDLAND MEDICAL SOCIETY, Birmingham Medical Institute, 154, Great Charles Street, Birmingham, 3
8.15 P.M. Prof. H. F. Humphreys: Reflections on World Health. (Valedictory address.)
ROYAL FACULTY OF PHYSICIANS AND SURGEONS, 242, St. Vincent Street, Glasgow.
5 P.M. Prof. Stanley Graham: Changing Pædiatrics.

Thursday, 6th

ROYAL SOCIETY OF MEDICINE
5 P.M. *United Services.* Surgeon Rear-Admiral S. G. Rainsford: Some After-thoughts of a Submarine Disaster.

Friday, 7th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. N. Asherson: Vertigo.
OSLER CLUB
8.15 P.M. (11, Chandos Street, W.1.) Professor Artelt: Samuel Thomas von Soemmerring (1755–1830).

Saturday, 8th

BRITISH ASSOCIATION OF ALLERGISTS
11.15 A.M. (King's College Hospital Medical School, S.E.5.) Autumn meeting.

Appointments

East Anglian Regional Hospital Board:

BEATTIE, J. W., M.D. Belf., M.R.C.P.: consultant physician in geriatrics, Norfolk and Norwich area.
BLACKISTON, P. H., M.R.C.S., F.F.A.R.C.S., D.A.: consultant anæsthetist, Newmarket and Bury St. Edmunds area.
POOL, K. R. S., M.B. Lond.: surgical registrar, Norfolk and Norwich Hospital.
RIXON, P. E., M.B. Aberd.: registrar in psychiatry, Hellesdon Hospital.
STEPHENS, J. P. M.CHIR. Camb., F.R.C.S.: consultant surgeon Norfolk and Norwich hospital group.
WILLIAMS, I. P., M.B. Camb., M.R.C.P., D.M.R.D.: consultant radiologist, Newmarket General Hospitals and Saffron Walden General Hospital.

Births, Marriages, and Deaths

BIRTHS

WILLIAMS.—On Sept. 23 at 155, Andover Road, Newbury, Berks, to Moza, wife of Dr. P. M. de C. Williams—a third daughter.

DEATHS

WHITEHEAD.—On Sept. 25 at 9, Lynton Park Road, Cheadle Hulme, Cheshire, Gordon Whitehead, M.B., the dearly loved husband of Molly (née Baker) and father of Gordon and John.

Notes and News

THE DRUG BILL

ADDRESSING the Essex branch of the British Medical Association at Colchester on Sept. 24, Dr. D. P. Stevenson, deputy secretary of the British Medical Association, said that from time to time there was criticism of the amount of medicine prescribed under the National Health Service. "Certainly," said Dr. Stevenson, "the cost is very heavy. Last year it was almost as much as the cost of the family doctor service itself (the actual proportion was four-fifths), but to make wild charges of overprescribing against the medical profession—as some of our critics do—is grossly unfair." There were several factors which the critics sometimes forgot. First, the cost of drugs had naturally shared in the general inflation of costs in the past seven years. Secondly, the cost of some of the most effective modern drugs was very high indeed. But if prescribing such drugs enabled an illness to be treated at home and prevented one more patient being sent to occupy an expensive hospital bed, was that not a positive economy for the country as a whole? This apart from the fact that the patient was enabled to return to work more quickly. Thirdly, the average age of the population was rising all the time; and older people, by and large, required more frequent treatment than younger persons. Fourthly, many members of the public believed that the regular consumption of certain drugs was necessary for their well-being. It was difficult for any individual doctor to combat this attitude, for the psychological benefits of the bottle and tablet were now well rooted in the public mind. The profession would welcome help by the press in decrying the idea that the problems of the twentieth century could not be faced without a bottle of medicine. Lastly, the critics of the general practitioner should, in fairness, put the cost of prescribing against the background of N.H.S. costs as a whole, especially the very heavy costs of the hospital service.

WORLD FEDERATION OF SOCIETIES OF ANESTHESIOLOGISTS

As reported on p. 669 of our last issue, this federation was formed during the World Congress of Anesthesiologists, held in Holland in September. Its foundation was the culmination of the work of a committee set up in Paris in 1951 under the chairmanship of Dr. Harold Griffith, of Montreal. The committee has throughout had the advice and help of Dr. J. F. Delafresnaye, secretary of C.I.O.M.S.

The federation started its independent life with a full meeting of the elected delegates from 26 national societies of anæsthetists, forming the general assembly. Also present were observers from societies which are not yet ready to become full members of the federation. Among these were official observers from the United States and Soviet Russia. Dr. Griffith was elected the first president, and Dr. Ritsema van Eck (Netherlands), Dr. A. Goldblat (Belgium), Dr. Rudolf Frey (Germany), and Dr. Manuel Gurbelo (Cuba) vice-presidents. Dr. Geoffrey Organe (London) was elected secretary-treasurer, and there is an executive committee of twelve including two representatives of the Association of Anæsthetists of Great Britain and Ireland.

The object of the federation, as summed up by the president at the opening session, is "to make available the highest standard of anæsthesia to all the peoples of the world." Among its detailed aims are disseminating scientific knowledge; recommending standards of training for anæsthetists; providing opportunities for postgraduate training and research; and establishing safety measures including the standardisation of equipment. The secretariat will be in London.

RESIGNATIONS FROM BOARD OF GOVERNORS

FIVE members have resigned from the United Oxford Hospitals Board of Governors because the Minister of Health has overruled a decision made by the board about the hospital organisation of the Radcliffe Infirmary. The members who have resigned include Dr. W. Ritchie Russell and Dr. Janet Vaughan. In announcing the resignations at a quarterly meeting of the board on Sept. 21,[1] Sir David Lindsay Keir, the chairman, said: "These are experienced and valuable colleagues, upon whose knowledge and judgment about hospital matters we have relied with confidence in the issues on which they have been asked to advise us. We all know the circumstances which led to their resignation have largely been outside the range of our own knowledge and certainly of our own control."

Four of the members who resigned were members of a committee which advised changes in organisation. Their recommendations were accepted by the board, but objections were made to the Minister of Health who, after appointing a small committee of inquiry to look into the matter, overruled the action proposed by the board. The board felt obliged to accept the Minister's decision, whereupon four members of the special committee and Dr. Ritchie Russell resigned in protest.

1. *Oxford Mail*, Sept. 21, 1955.

SUPERANNUATION SCHEME

THE National Health Service (Superannuation) Regulations, 1955, which come into effect on Oct. 1, consolidate the previous regulations dealing with the National Health Service superannuation scheme, and make a substantial number of amendments, many of which are consequential on the Local Government Superannuation Act, 1953, and the Local Government Superannuation (Benefits) Regulations, 1954.

The regulations contain special provisions relating to persons holding more than one appointment simultaneously in the hospital or general-practitioner service. They provide that all superannuable service can reckon towards benefit unless there has been a disqualifying break of a year without any superannuable health service appointment being held; that for benefit purposes a medical or dental practitioner on the list of more than one executive council shall be treated as though he were on a single combined list; and that a person who, on giving up one part-time employment at or after the minimum retiring age for pension, ceases to be superannuable in respect of a continuing part-time employment, shall have his superannuation rights in the latter preserved. Revised provisions with respect to the remuneration reckonable for superannuation purposes by medical and dental practitioners are included. These enable medical practitioners practising in partnership to have their remuneration as practitioners allocated between them in agreed proportions which may, if they so elect, take account of remuneration from hospital employment.

REMUNERATION OF BIOCHEMISTS AND PHYSICISTS

Professional and Technical Whitley Council A has agreed on increased salary-scales for full-time biochemists and physicists who are not medically qualified and are employed in laboratories and scientific departments of hospitals in the National Health Service. The scales are as follows:

Basic grade.—Probationary period: (*a*) with 1st or 2nd class honours degree or, for biochemists only, A.R.I.C., £525 × £25–£625; (*b*) other entrants, £475 × £25–£575. After probationary period: £650 × £30(3) × £35(3)–£845.
Senior grade.—£910 × £40(8)–£1230.
Principal grade.—£1280 × £50(5)–£1530.
Top grade.—Minimum of £1600, 4 increments of £75.

W.H.O. IN EUROPE

THE W.H.O. Regional Committee for Europe, at a session in Vienna on Sept. 5–8, concluded that in Europe inter-country programmes are the most appropriate method of helping governments to strengthen their health services. In the years 1957–60 the main aims will be to study common health problems and exchange information, and to develop training facilities for medical and health personnel. The committee decided that work on chronic diseases should be developed, and that greater attention should be given to the prevention of accidents. The European regional office is to be established in Copenhagen, possibly in April, 1957.

REHABILITATION IN BRIEF

THE Luton and Dunstable Hospital has produced an excellent booklet[1] based on seven years' experience in its rehabilitation centre. The conclusions of its rehabilitation team—including doctors, physiotherapists, workshop engineer, and almoner—are set out crisply in eight "principles of rehabilitation," illustrated by well-chosen photographs.

The first principle is "getting well is a full-time job," and a day's time-table for three typical patients is shown. As a means of promoting remedial movement, engineering workshop practice has been found far superior to the "arts and crafts" of the average physiotherapy department: equipment can be modified to exercise any group of muscles, and the competitive atmosphere of the workshop restores the patient's confidence. Local industries coöperate by giving machinery, as well as by providing a constant supply of suitable work.

1. Principles of Rehabilitation as Practised at the Luton and Dunstable Hospital, Luton, Bedfordshire. 1955. Pp. 23.

The patient's progress is recorded regularly (some of the instruments for this have been improved in the hospital), and whenever possible the date of his return to work is forecast early and precisely to the advantage alike of patient and employer. "Since all the patients attending the centre have some major disability, it is essential to make early plans for resettlement so that anxiety may be allayed and energy freed to allow full participation in treatment." Visits to the centre by personnel managers to mark progress and discuss future plans are common and welcome.

The physician or surgeon who has looked after the patient in the hospital follows his treatment through the centre, and his ideas on treatment are often influenced by the opinions of the non-medical members of the team, all of whom are present at the weekly clinic held in the workshop and at set conferences.

In 1953–54 the average daily attendance was 26, and the average length of stay four weeks. Enlargement of the centre is hopefully projected.

TUMOUR PATHOLOGY

THE five latest fascicles of the *Atlas of Tumor Pathology*,[1] which is being compiled under the auspices of the Division of Medical Sciences of the National Research Council at Washington, contain, like the previous ones, much information and opinion valuable to clinicians as well as pathologists.

Tumors of the Soft Tissues[2]

Professor Purdy Stout analyses the findings in 1349 malignant and 7337 benign mesenchymal tumours which have been examined at Columbia University during the last forty-five years. The histological analysis of these groups is of interest, but the proportion of malignant to benign tumours in the series is regarded as unrepresentative because consultations are more often sought on malignant than on benign tumours.

Tissue-culture has proved helpful in the study of many of these tumours, and the author makes several references to the work of his colleague Dr. Margaret Murray: obscure tumours of mesoblastic origin can sometimes be identified, he says, because, however anaplastic they may be, explants grown in vitro sufficiently resemble their normal prototype to be recognised. Dr. Stout adheres to the myoblastic view of the granular-cell myoblastoma because of the evidence of tissue-culture studies; but he advises a guarded prognosis, for in his experience 4 such tumours with a relatively benign appearance have metastasised.

He holds that if the pathologist properly fulfils his function he will be prepared to advise the surgeon on the probable behaviour and the best form of treatment of any tumour encountered. The best chance of eradicating a malignant tumour of the soft tissue lies in the hands of the man—be he surgeon or radiotherapist—who makes the first attempt; so an accurate biopsy is essential. It is worth noting that Dr. Stout seldom finds it possible to report sufficiently accurately on a frozen section; he prefers to wait a day or two for paraffin sections.

His text is supported by 78 first-class illustrations.

Tumors of the Major Salivary Glands[3]

Dr. Foote and Dr. Frazell review 900 cases of salivary-gland tumours from the records of the Memorial Centre in New York: these included 447 benign and 46 malignant mixed tumours of the parotid gland and 47 benign and 11 malignant mixed tumours of the submaxillary gland. There were none of the sublingual gland. Almost 60% of the cases were in women, but there was no detectable familial tendency. The authors are among those who believe that the mixed tumours arise from adult epithelium, there being in their experience sufficient evidence of gradual metaplasia of such cells into the chondromyxoid and chondromatous components so characteristic of these tumours.

The recurrence-rate for the benign tumours initially treated at the Memorial Hospital was only 2·13%; this surprisingly low figure probably (as is pointed out) reflects "surgical performance within a specialised head and neck surgical department." Prolongations of growth sometimes extend beyond the apparently limiting capsule, and it is these overlooked excrescences which explain the failed attempt at eradication.

The malignant mixed tumours have a long history, and the average age of patients when first seen is over ten years higher than in the benign tumours: for these and other reasons the authors believe that the malignant tumours arise from tumours which are initially benign. The duration of life from the onset of symptoms in these cases varied from under one to forty-three years. Some of these tumours may present in the first sections as a salivary-gland carcinoma, and it is only after extensive search that one finds histological evidence of a mixed tumour. This, Foote and Frazell believe, accounts for the infrequency with which malignant mixed salivary-gland tumours are reported: indeed they speak of having examined as many as 100 blocks from a single bulky tumour before the evidence was found; and "on other occasions, even after very extensive study positive evidence could not be produced, although we strongly suspected that a benign mixed tumor had formerly existed."

Their 180 illustrations, of consistently high standard, include many examples of the malignant mixed tumour, and two from a case of histologically benign mixed tumour which metastasised to the lung.

Tumors of the Stomach[4]

Carcinoma accounted for 72·2% of the 651 cases of gastric tumour passing through the laboratories of the surgical division of Columbia University. When one realises that the inoperable carcinomas are excluded from such a series, the relative rarity of benign tumours of the stomach becomes apparent. While gastroscopy, radiography, electrogastrography, and exfoliative cytology are all important aids in diagnosis, none of them is decisive in every case: so far as the last of these procedures is concerned, Professor Stout sees promise for the future in the abrasive-balloon technique. Not only is it sometimes impossible to distinguish the benign from the malignant ulcer by the diagnostic procedures at our command, but a benign and a malignant ulcer may on removal closely resemble each other. Gastritis polyposa may be a precancerous condition, but the author remains in doubt as to the importance of atrophic changes in the mucosa. Chronic peptic ulcer was found in 7·2% of the stomachs resected for carcinoma, and in several of these the cancer could be found along one of the edges of the ulcer. Linitis plastica was found in only 4·5% of the cases of carcinoma. Instances of multiple carcinoma of the stomach were seen both in patients with multiple polyps and in those without. One case is reported where a man developed an apparently new infiltrating carcinoma in the remaining gastric pouch twenty-three years after partial gastrectomy for fungating carcinoma.

Professor Stout recommends that leiomyomas, when diagnosed, should be removed because they may at any time cause serious hæmorrhage or become malignant. The behaviour of a lymphosarcoma is unpredictable: it may be either resected or treated with X rays. He recalls one case in which the growth was incompletely removed and no further treatment was given: yet there was no recurrence during the nineteen remaining years of the patient's life.

Tumors of the Retroperitoneum, Mesentery, and Peritoneum[5]

Professor Ackerman deals with the interesting group of tumours arising from, or in connection with, the mesentery and peritoneum. The Columbia University figures collected by Stout show that over a period of fifty years there were 265 malignant as against 75 benign tumours in the retroperitoneal spaces. Of the malignant types, lymphosarcoma, liposarcoma, leiomyosarcoma, Hodgkin's disease, and embryonal carcinoma occurred in that order of frequency, while of the benign tumours cysts of the caudal gut, phæochromocytoma, and granular-cell myoblastoma were the most frequently observed. In this beautifully illustrated monograph, Professor Ackerman pays special attention to mesotheliomas of the peritoneum, slightly more than two-thirds of which appear to be malignant; he shows how readily they may be mimicked in the female by a serous cystadenoma of the ovary. The "consummate ability of mesothelial cells to simulate carcinoma" is the subject of special consideration: the illustration of exfoliated pseudo-acini, simulating metatastic carcinoma, in the ascitic-fluid deposit from a case of cirrhosis hepatitis is particularly instructive.

1. Obtainable from the Subcommittee on Oncology, Armed Forces Institute of Pathology, 6825, 16th Street, N.W., Washington 25, D.C., U.S.A.
2. Fascicle 5. By ARTHUR PURDY STOUT, M.D., professor of pathology, Columbia University, New York. 1953. Pp. 138. $2.00.
3. Fascicle 11. By FRANK W. FOOTE, jun., M.D., attending pathologist, and EDGAR L. FRAZELL, M.D., Memorial Centre for Cancer and Allied Diseases, New York. 1954. Pp. 149. $1.50.
4. Fascicle 21. By Prof. A. P. STOUT. 1953. Pp. 104. $1.75.
5. Fascicles 23 and 24. By LAUREN V. ACKERMAN, M.D., professor of pathology and surgical pathology, Washington University, St. Louis, Mo. 1954. Pp. 136. $1.50.

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